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INTRINSIC (NONALLERGIC) BRONCHIAL ASTHMA AS A MANIFESTATION OF FIBROCYSTIC DISEASE OF THE PANCREAS

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FIBROCYSTIC disease of the pancreas (mucoviscidosis) has been well established as a disease entity only within the past two decades. Meconium ileus in the newborn and chronic bronchopneumonia in the older infant are examples of the variants seen in this disorder. Early in the disease repeated, rather severe, bouts of upper and lower respiratory tract infection are noted. Generally, vigorous treatment with potent antibiotics will lead to temporary improvement. As the patient grows older, the frequency of such infections, which may be associated with asthmatic symptoms, increases. In thirty-three of our sixty-eight patients who suffered from this grave constitutional disorder, asthmatic findings were prominent. We have thought it worth while to emphasize these findings and to attempt an explanation.

CASE REPORT

The patient was G. J., a 2-year-old boy. Starting soon after birth, it was noted that he had frequent large, foul stools. His abdomen seemed large in proportion to his body size. He gained weight poorly. At the age of 10 months he developed what was considered elsewhere to be an allergic cough. At 1 year of age he weighed only 19 pounds and the parents were told that the poor weight gain was due to food allergy. He was taken off the evaporated milk formula which he had received all his life and was given skimmed milk; later, he received a higher-protein proprietary formula. During his second winter he had almost constant bronchitis. When seen by us, his general appearance was that of a small but fairly well-proportioned 2-year-old boy. Duodenal intubation yielded only a small amount of viscid alkaline juice, which contained no tryptic activity. The parents called attention to the

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boy's wheezing respiration, which they had observed on frequent occasions during the past year. Within ten minutes after epinephrine was given hypodermically, there was complete disappearance of wheezing and respiratory distress. He died one month later; autopsy confirmed fibrocystic disease of the pancreas, acute bronchitis, bronchopneumonia, and emphysema.

DISCUSSION

Factors known to cause impairment of pulmonary function in asthma are bronchospasm, edema of bronchial mucous membranes, and retention of excessive mucus, often tenacious. The relative importance of these factors is not known. The clinical symptoms and signs may be the same, whether the asthmatic state is a result of extrinsic allergic factors or of pulmonary infection, as it occurs in mucoviscidosis. Kramer, in discussing Andersen's[3] history-making paper of 1938, alluded to two children with wheezing and cough and said *inter alia*: "... the terminal condition began with *asthmatic bronchitis*. ..." Of the patients studied by Abbott, McCreary, Pocock, and Brown,[1] 80 per cent had respiratory tract symptoms and signs; wheezing was heard in 10 per cent and, when present, it was conspicuous. Bodian[8] observed wheezing in thirteen of his 116 cases, an incidence of about 11 per cent. Other instances of wheezing have been reported.[6-11, 13, 15, 16, 18-27]

Evidence for bronchospasm is twofold. The dramatic response of the asthmatic state in several of these children when epinephrine was administered by experienced pediatricians certainly is impressive. Moreover, the bronchograms reproduced herewith from one of our patients show several areas of narrowing of the sort stressed by di Rienzo.[12] Similar findings have been obtained in bronchograms from other of our patients with fibrocystic disease.

Bronchial mucosal edema of an inflammatory nature, as well as thick tenacious mucus, is often seen in Fig. 1. This mucus has received much attention. Andersen[4] stated: "... the mucus secreted by the bronchial glands is abundant and viscous but does not differ morphologically from that seen occasionally in other types of cases, notably in patients dying during an attack of asthma ... it can be seen to extend from the ducts of the mucus glands in the same way that it does in cases of asthma." Farber[14] also commented on hyperexpansion of the lungs, the result of partial obstruction in the trachea, the bronchi, and the bronchioles caused by the thick tenacious mucoid and mucopurulent exudate. "At times the impression was gained that the patient finally must have experienced suffocation because of the abundance and tenacity of the mucopurulent exudate in the upper respiratory tract."[14]

Bronchoscopy also disclosed features similar to those of asthma. Thus, Atkins[5] remarked concerning his patients with fibrocystic disease that: "... the hyperemic bronchus shows marked expiratory intrusion of the posterior bronchial wall into the lumen producing crescentic cross section to the bronchus. In this respect the bronchus resembles that seen in the asthmatic patients." He further observed that the reduction of pulmonary reserve was manifested by the frequency and severity of cyanosis during bronchoscopy.

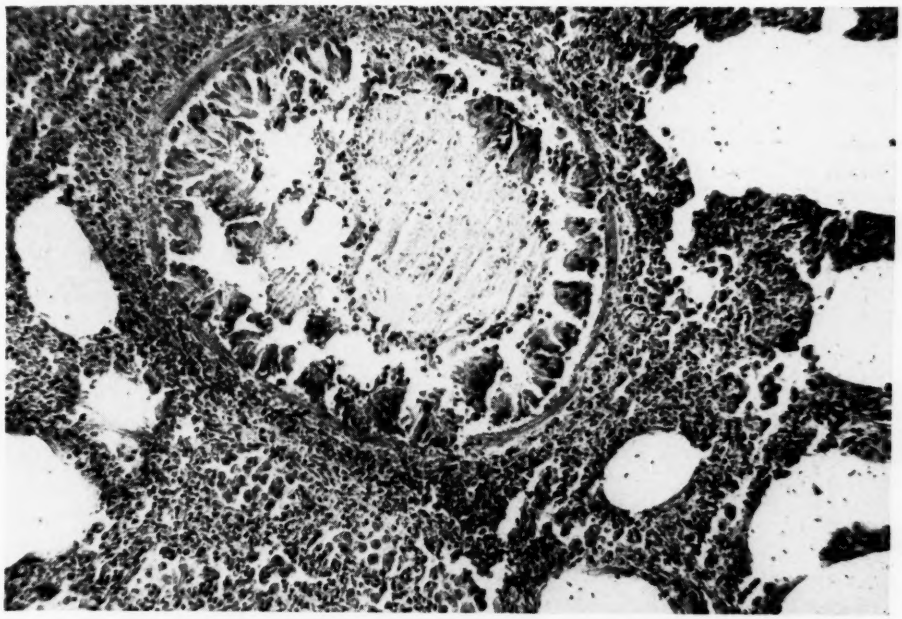

Fig. 1.—Bronchiole with inspissated mucus, desquamation of bronchial mucosa, and peribronchial inflammation with neutrophils, and a few eosinophils. Hypertrophic peribronchiolar musculature. (Magnification ×135.)

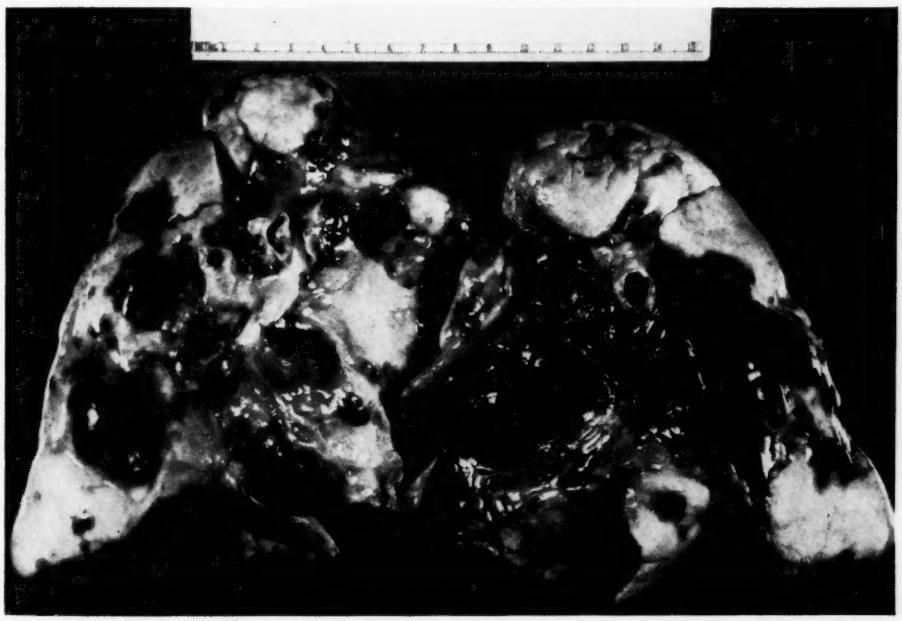

Fig. 2.—View of the gross pathology of lungs from patient who died of fibrocystic disease. The white areas indicate zones of emphysema. The dark areas represent sites of atelectasis and pneumonitis.

It is relevant to cite the studies of Kaye, Whittenberger, and Silverman[17] on respiratory air flow patterns in children. They found abnormal air flow patterns of a rather uniform type in patients with a variety of diseases affecting the lungs. "In children the same pattern was found in subjects with asthma . . . and severe pulmonary disease associated with fibrosis of the pancreas."

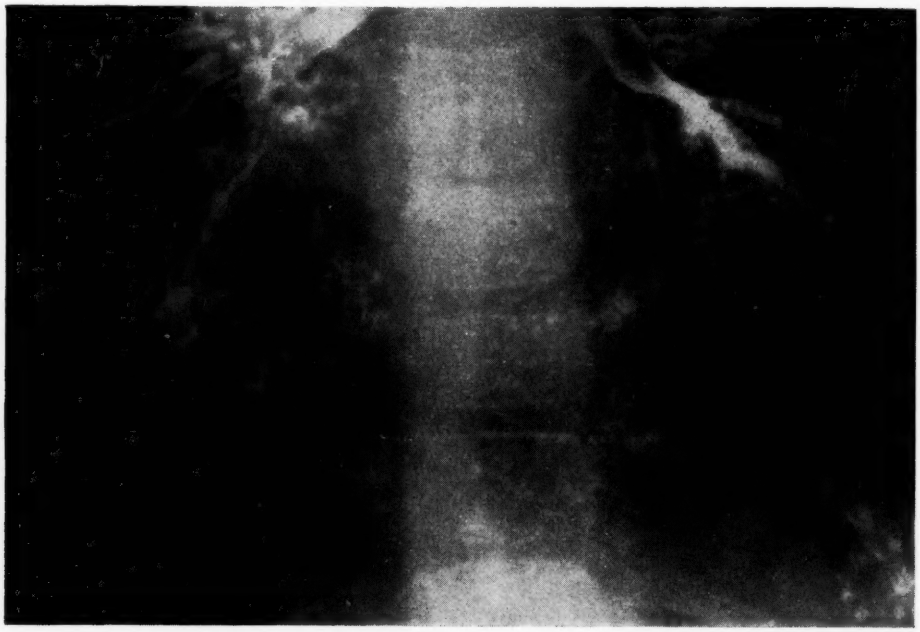

Fig. 3.—In this bronchogram areas of bronchial obstruction may be seen, in part due to bronchial constriction and in part due to filling with mucus, pus, and cellular debris.

SUMMARY AND CONCLUSIONS

Intrinsic bronchial asthma is customarily defined as a symptom complex of cough, dyspnea, and wheezing caused by bronchospasm, bronchial mucosal edema, tenacious sputum, and usually respiratory tract infections. Evidence is given to support the contention that these exist in a significant proportion of children with fibrocystic disease of the pancreas. This disease should be excluded whenever bronchial asthma is a conspicuous feature in young patients.

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ALLERGY TO CADDIS FLY (TRICHOPTERA)

II. Clinical Aspects

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THE caddis fly (*Trichoptera*) has been recognized as an excitant of allergic respiratory symptoms for nearly thirty years. Since no reports on caddis fly allergy have appeared in the literature for many years, a résumé of my clinical experience with this type on the Niagara frontier has seemed opportune.

The head of the Niagara River as it emerges from Lake Erie is heavily infested by these flies. Because of the location on either side of the river of two cities—Fort Erie, Canada (population 9,200) and Buffalo, New York (population 600,000), a large human population has been exposed to their emanations. The residential section of Fort Erie extends to the water's edge and the principal larval beds of the flies lie on the river bottom along the Fort Erie front. As a result, exposure to the flies in Fort Erie has been much greater than in Buffalo.

THE INSECT

The *Trichoptera* are aquatic insects which live in fresh water, except in the adult (reproductive) stage. The wings of the adult are covered with microscopic hairs (setae) which are very easily dislodged. These hairs, and to a less extent the dried particles of their dead bodies, are airborne and, by inhalation, induce the allergic symptoms. They are not biting insects.

Along the Niagara River, the adult flies appear about mid-June and persist until the end of September, the contiguous land being more or less continuously infested for a distance inland of several hundred yards. At irregular intervals during their season, usually in the late afternoon and evening, the insects may form great swarms extending a mile or two along the banks and inland up to one-half mile. Such swarms may contain many millions of individual flies and may persist for several days.

For a detailed discussion of the classification, distribution, and habits of the *Trichoptera*, I would refer to my earlier article[1] which appeared in the March, 1957, issue of The Journal of Allergy.

THE CADDIS-FLY-SENSITIVE PATIENT

The emanations (setae and body particles) of the caddis fly are intrinsically innocuous; normal persons are not affected by them, even on heavy exposure. Persons allergic to these insects exhibit all the symptoms that are characteristic of respiratory allergy: nasal, conjunctival, and bronchial. I have seen no case of atopic or contact dermatitis in which sensitivity to the caddis fly appeared to be causally related.

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Of the fifty-seven patients considered below, in whom treatment with caddis fly extract seemed indicated, thirty were males and twenty-seven were females. The youngest was 6 years old and the oldest was 57 years old when they first came under my observation. There were seven children 10 years of age or younger, fourteen persons between the ages of 11 and 20 years, ten between the ages of 21 and 30 years, eighteen between the ages of 31 and 40 years, six between 41 and 50 years, and two over 50 years. All were white.

The following description is a synthetic picture based on the patients in my experience who were unequivocally allergic to caddis fly and in whom this fly was the primary excitant of their symptoms.

The patient has experienced fairly marked exposure to the caddis fly for several years, some as much as thirty years, before the symptoms first appear. The early symptoms may be typical vasomotor rhinitis, mild asthma, or both. As the succeeding seasons recur, the symptoms increase in intensity; conjunctival itching and redness are more pronounced than in pollinosis; nasal obstruction is very troublesome. Asthma is a more frequent symptom than in pollinosis, and is often severe. These symptoms appear about mid-June and become marked by the end of June in the Niagara area, when the first dense swarms of the flies occur. During the rest of the summer the symptoms persist, at least in mild degree, with exacerbations coincident with fluctuations in the concentration of the flying insects, and are marked during the periods of the swarms. As the concentration of the flies decreases during September, the symptoms ameliorate and usually cease by the end of September. During the season, the patient can secure marked, and often complete, relief of symptoms by going inland five or six miles from the river. Several patients have arranged to sleep thus far away during the heavy swarms. A number of patients who have moved to a place of residence six to eight miles or more away from the river have discontinued treatment entirely.

From the end of September until the following June, the patient is symptom free. However, it has often happened that a patient has entered an attic or a boathouse during the interval between the caddis fly seasons and has developed typical symptoms when he has stirred up the dead flies lying there, as the insects find their way through any house opening during the summer swarms.

Adequate hyposensitizing treatment has resulted in good control of the symptoms,[4, 5] particularly of the asthma. Most treated patients still experience some nasal and eye symptoms during the season when the flies are thick, if they remain in the areas of heavy infestation, but can control these symptoms with antihistaminics.

One case, unique in my experience, is that of a 12-year-old boy who had mild perennial vasomotor rhinitis, but who developed repeated corneal ulcers only during the caddis fly season. He showed a very marked skin reaction to caddis fly, a slight reaction to feathers, and negative reactions to pollens, May fly, molds, inhalants, and foods. Perennial hyposensitizing injections relieved the corneal ulcers.

ATOPIC CHARACTERISTICS

As Parlato[2, 3, 5] and I[4, 6] have shown, direct skin tests with an extract of the whole fly yield immediate, wheal type reactions in persons allergic to the caddis fly. Specific reagins to caddis fly are demonstrable in the patient's blood serum by the Prausnitz-Küstner method.[2-4, 7] Positive conjunctival tests are obtained with both the wing hairs and body particles, as well as with the extract.[2-4] Typical symptoms can be induced by the deliberate inhalation of the hairs and body particles.[2-4]

Some years ago I succeeded in inducing nonfatal anaphylactic symptoms in a small number of guinea pigs, using caddis fly extract for the sensitizing and shocking doses. The study was not completed, but apparently a large dose of the antigen is required to produce high sensitization.

The antigen in the extract of the whole fly appears to be multiple, since extracts from separate species of caddis fly have been shown to contain both common factors and differing factors.[6]

COLLECTION OF THE INSECTS AND PREPARATION OF THE EXTRACT

The caddis flies may be secured in quantity by means of a large trap, lighted inside with all but the mouth shaded and set at dusk adjacent to the water's edge. They also may be caught alive with a wide-mouth (24 inch) conical net made of cotton mosquito netting. By repeated air sweeps, as the flies swarm over bushes in daylight or around outdoor lights in the evening, the insects accumulate at the tip of the cone and are killed by inserting the tip into a wide-mouth jar containing carbon tetrachloride. In my experience, the net method has yielded a supply somewhat less contaminated with other insects than the trap. Supplies of dead caddis flies swept up from surfaces beneath outdoor lights have usually been so contaminated with other insects and dirt as to be nearly worthless. Whatever the method of securing them, the catch is usually a mixture of several species of caddis fly.

After collection, the flies are spread out thinly on a clean surface for two or three days to dry. They are then carefully sorted to remove extraneous insects (moths, beetles, May flies, flying ants, etc.), and in addition may be sifted to remove gnats, mosquitoes, and midges. The whole flies are defatted (an astonishing amount of fatty material is removed), and extracted in Coca's solution. The extract is sterilized by Seitz filtration, tested for sterility, and stored at refrigerator temperature.

Standardization has been done on the protein nitrogen basis (phosphotungstic-acid-precipitable nitrogen method of Cooke and Stull[12]). The initial extract is made up on a 10 per cent basis: 10 grams of dried defatted flies to 100 c.c. of extracting fluid. The protein nitrogen content of this extract has averaged about 0.30 mg. per cubic centimeter.

If the defatted flies are to be preserved in the dry state for future extraction, they should be protected from moisture by an efficient desiccating method which will also prevent moldiness, to which they are prone. They should be kept in a refrigerator.

SKIN TEST TECHNIQUE

Skin testing has been done by the intradermal method, using dilutions of the extract containing 10 units, 100 units, and 1,000 units of protein nitrogen per cubic centimeter. These strengths correspond, roughly, to 1:30,000, 1:3,000, and 1:300 dilutions, respectively, on the weight-to-volume basis. The extract is not intrinsically irritating when used in appropriate dilutions.

In addition to the caddis fly, patients whose allergic symptoms were limited to the summer months have been routinely tested with pollens, four mold spores (alternaria, aspergillus, hormodendron, penicillium), and frequently May fly. Patients with perennial symptoms have also been tested with the usual inhalants and common foods.

CLINICAL MATERIAL

The material for this report is based on the case records of 623 private allergic patients whom I have skin tested with caddis fly extract since 1940. Patients tested prior to that date have been excluded, since their full records are no longer available.

These 623 patients represent, to some extent, a selected group, because I have tested with caddis fly those patients in whom some exposure to the insects has seemed to me a possibility; on the other hand, I have *not* always tested with caddis fly the many patients in whom such exposure seemed improbable or nonexistent.

RESULTS OF SKIN TESTS

Of the 623 patients, 236 gave no skin reaction to caddis fly and 172 gave a slight reaction only to the strongest test dilution. A moderate reaction to the strongest test dilution was obtained in 141 patients and a marked reaction was obtained in seventy-four patients. Thus, 215 patients showed definite skin sensitivity to the flies and 408 showed negative or indeterminate reactions (Table I).

TABLE I. RESULTS OF INTRADERMAL TESTS WITH CADDIS FLY

REACTION	NUMBER OF PATIENTS		PER CENT	
Negative	236	408	37.9	65.5
Slight only	172		27.6	
Moderate only	141	215	22.6	34.5
Marked or greater	74		11.9	
	623		100.0	

The incidence of definitely positive skin tests (moderate and marked) of patients living in the immediate vicinity of the Niagara River and of others living twenty miles or more distant appears in Table II. These figures show a definite decrease in the occurrence of stronger skin test reactions with the increase in distance of residence from the known area of concentration of the flies.

TABLE II. RELATIONSHIP BETWEEN PLACE OF RESIDENCE AND INCIDENCE OF DEFINITELY POSITIVE SKIN TESTS TO CADDIS FLY

RESIDENCE	NO. OF PATIENTS TESTED	PATIENTS WITH MODERATE OR MARKED TESTS	PER CENT
Fort Erie; heavy exposure	37	22	60
Buffalo and on Niagara River within 10 miles of larval beds; moderate to light exposure	279	99	35
Inland more than 20 miles from larval beds, and not on other large streams or lakes; little or no exposure	142	31	22

As would be expected in allergic persons, no patient has been observed who gave a positive skin test solely to caddis fly. All have reacted weakly or strongly to a few, to several, or to many of the other allergens included in the series of tests applied.

The interpretation of a definitely positive (moderate or marked) skin test to caddis fly in a given patient presents the same problems as in the case of any pollen or other inhalant allergen. Since the caddis fly extract is not intrinsically irritating in the dilutions used, we must assume that, to develop this skin sensitivity, such a patient has been exposed at some time to caddis fly or *to some other insect which is related antigenically to the caddis fly.*

TREATMENT

The circumstances of history, seasonal symptoms, and exposure to the insects made advisable the treatment by hyposensitization of fifty-seven patients out of 387 patients who yielded a positive skin test (slight or greater) to caddis fly. Of these fifty-seven patients, twenty-four resided in Fort Erie where the exposure is heavy and ten resided in Buffalo. The remaining twenty-three patients resided in an area within twenty miles of the head of the Niagara River and were exposed by their not infrequent trips into the infested area.* These patients have been grouped in Table III according to the relative importance of the caddis fly in the production of their symptoms.

TABLE III. CADDIS FLY FACTOR IN PRODUCTION OF SYMPTOMS IN TREATED PATIENTS

GROUP	IMPORTANCE OF CADDIS FLY FACTOR	NUMBER OF PATIENTS
A	Caddis fly primary	6
B	Caddis fly a major factor	4
C	Caddis fly, pollens, etc., about equal	10
D	Caddis fly minor	37

No patients have been observed in whom the caddis fly was the sole excitant of their symptoms, and therefore there are none in whom treatment with caddis fly extract alone appeared justified. In addition to caddis fly,

*A questionnaire addressed to the leading allergists in Buffalo in November, 1956, disclosed that they had sixty-three patients currently under hyposensitization with caddis fly. With my own current patients, there were eighty-four patients under treatment at that time in our area.

fifty patients were treated with one or more pollens, thirty-two with one or more molds, nineteen with May fly, and forty-four with house dust or other inhalants.

The initial dose of the caddis fly extract has been 2 to 10 protein nitrogen units. The maximum dose reached has been between 500 and 10,000 units, and this dose has been continued every four weeks on a perennial basis. The duration of treatment in each patient has ranged from nine months to over seventeen years. Nine patients have been treated for over twelve years. Excluding eleven patients who received treatment for less than two years, there are forty-six patients whose treatment period has averaged a little over seven years. Twenty-one patients are still under treatment, with the duration of treatment ranging from one and one-half years to over seventeen years and an average period of just over six years.

The incidence of local and constitutional reactions attributable to the caddis fly extract has been about the same as in pollen treatment. Both have occasionally been marked, although I have met with no dangerous general reactions.

The results of treatment in these fifty-seven patients are shown in Table IV.

The effectiveness of hyposensitization with caddis fly extract can be judged, I believe, only in the ten patients in Groups A and B, as the picture becomes complicated by allergy to other substances in Groups C and D, and the results could be attributed largely to the treatment with the other extracts used. These ten patients (nine from Fort Erie and one from Buffalo) all resided within a few hundred yards of the river's edge.

TABLE IV. RESULTS OF TREATMENT WITH CADDIS FLY

GROUP	NUMBER OF PATIENTS			TOTAL
	GOOD	FAIR	POOR	
A	4	1	1	6
B	2	2	0	4
C	9	1	0	10
D	21	10	6	37

The one patient in Group A who yielded a poor result was very sensitive to caddis fly, by which he was surrounded during his working hours as a Canadian inspector at the Peace Bridge. He gave strong skin reactions to caddis fly and to house dust, but negative skin reactions to all the pollens and other inhalants and only mild reactions to one mold and to May fly. The dust was included in his injections with caddis fly. He could secure practically complete relief of symptoms during the caddis fly season by going five or six miles inland. After twenty months of perennial injections, with poor protection from the caddis flies at his work, he was transferred to another area free of these flies.

POSSIBLE ANTIGENIC RELATIONSHIP BETWEEN CADDIS FLY AND OTHER ALLERGENIC INSECTS

The diagnosis and treatment of allergy to the caddis fly present no particular problems in patients skin positive to these flies who reside or vacation in areas where the flies are abundant. In the combination of typical symptoms

coinciding with the caddis fly season, a positive skin test, and demonstrable exposure to the flies, one will have reasonably secure grounds on which to base the diagnosis and the decision as to specific treatment.

A more difficult situation is that met with in the patient who is skin positive to caddis flies but who is not, so far as is known, exposed to any concentration of them. This situation requires some discussion.

Pertinent to this problem is allergic sensitivity to May fly (*Ephemerida*), which Figley[9] reported in 1929, and to butterflies and moths (*Lepidoptera*), reported by Parlato[7, 8] in 1932 and by Urbach and Gottlieb[10] in 1941.

In my group of 623 cases, 196 patients yielding moderate or marked reactions to caddis fly were also tested with May fly extract in comparable dilutions (Table V). The May fly occurs to some extent in the immediate Niagara area, and is abundant along the sandy shores of Lake Erie three or four miles distant, so that exposure to this insect is probably common among the population of the region.

TABLE V. COMPARABLE SKIN REACTIONS TO MAY FLY IN 196 PATIENTS SKIN POSITIVE TO CADDIS FLY

COMPARATIVE SKIN REACTIONS TO CADDIS FLY AND MAY FLY	PER CENT
Caddis fly test the stronger	43
Caddis fly and May fly test about equal	32
May fly test the stronger	17
May fly test negative	8

The caddis fly is distributed over all the nonarid regions of North America. In addition to sites of heavy infestation, it is found in many brooks, streams, and small rivers, and can be seen near their banks. But it is not evident in the gardens, fields, and woods elsewhere in the countryside. Parlato, LaDuca, and Durham[11] found no caddis fly hairs on slides exposed more than six miles from the Niagara River, in spite of their great abundance at the river's edge. Exposure to caddis fly emanations of the general human population residing away from areas of its local concentrations must, therefore, be minimal. In my own experience, this minimal exposure is insufficient to cause symptoms in a patient unequivocally allergic to caddis fly. I believe that a relatively intense exposure is necessary to induce sensitivity to caddis fly and to excite allergic symptoms.

The May fly (*Ephemerida*), an aquatic insect except in the adult stage, is locally abundant in many areas, but is found only in the immediate vicinity of the water's edge. It develops in quiet bodies of water, such as ponds, lakes, and slow-flowing streams. Many people in lakeside cities and at fresh-water beaches and summer resorts are exposed to the dried and powdered pellicles of this insect.

In contrast to the sparsity of caddis flies and May flies in the general countryside are the ubiquitousness and relative abundance of butterflies and moths *(Lepidoptera).* Human exposure to the emanations of the *Lepidoptera* must, therefore, be much more common than to those of the *Trichoptera.*

From the preceding, it follows that human exposure to the *Lepidoptera* must be quite general. Exposure to the *Ephemerida* and the *Trichoptera* is

less widespread and is rather "spotty." Nevertheless, light exposure to the latter two orders cannot be entirely ruled out, except in arid and semiarid regions.

The coincidence of positive skin tests in the same patient to *Trichoptera* and *Lepidoptera,* reported by Parlato,[7] and to *Trichoptera* and *Ephemerida,* reported in the present article, may be interpreted, on the one hand, as the coexistence in the patient of separately specific sensitivities to the different insects or, on the other hand, as true relationships between the antigens of the three orders, with all the implications such relationships would present. Taxonomically, the *Trichoptera* and *Lepidoptera* are not too far removed from each other; hence, antigenic relationship may not be improbable. The *Trichoptera* and *Ephemerida* are further apart biologically, so that antigenic relationship between them may be less likely. This problem certainly demands further careful investigation using modern experimental techniques—biologic, immunologic, and immunochemical—for studying the relationships between the antigens.

SUMMARY

A brief note is presented on the caddis fly as it occurs in the Niagara area. Directions are given for the collection and preservation of the insects and for the preparation of the extract. The typical caddis-fly-sensitive patient is described.

Skin tests with caddis fly extract were done on 623 patients suffering from symptoms of respiratory allergy. Of the total group, 34.5 per cent yielded definitely positive (moderate or marked) reactions and 65.5 per cent yielded indeterminate (slight) or negative reactions. However, 60 per cent (twenty-two out of thirty-seven) of the patients living in the immediate area of heaviest infestation (Fort Erie) showed moderate or marked reactions. The occurrence of these strong reactions decreased markedly as the distance of residence of the patients from the infested area increased and the exposure became less.

Fifty-seven patients skin positive to caddis fly have been treated with hyposensitizing injections of the extract. In ten of these, the caddis fly was the dominant factor in causing their symptoms; all ten lived in the immediate vicinity of the infested area. In the remaining forty-seven patients, other allergens (pollens, molds, May fly, etc.) were dominant, but caddis fly extract was also used in treatment because of known exposure.

The problems presented by the numerous patients who were definitely skin sensitive to caddis fly but who were not exposed to their emanations, so far as known, are discussed. The frequent occurrence of crossed skin reactions in a given patient to caddis fly, May fly, and to butterflies and moths raises the question of antigenic relationship between these separate orders of insects.

CONCLUSION

In the general countryside exposure of the human population to caddis fly emanations is insignificant. In the immediate area of heavy infestation by caddis flies, however, allergic sensitivity to this insect is quite frequent. Allergists should investigate the possible presence of these insects in the regions from

which they draw their patients and, if the insects are found in appreciable numbers, cases of caddis fly allergy should be anticipated and caddis fly extract should be included in their skin testing series.

From a practical point of view, and considering our present lack of knowledge regarding the antigenic relationships between *Trichoptera, Lepidoptera,* and *Ephemerida,* I believe that specific hyposensitization with caddis fly should be undertaken in a patient skin positive to the insect only on the basis of known exposure.

Because of the fairly frequent occurrence of positive skin tests to caddis fly in patients having no known exposure to them, and because of the frequent crossed reactions in a given patient to the above three orders of insects, careful studies should be made with modern experimental techniques to determine whether these crossed reactions indicate the coexistence of immunologically separate sensitivities or antigenic relationships between the three orders.

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THE ENHANCEMENT OF INFECTION WITH STAPHYLOCOCCUS AUREUS IN MICE SENSITIZED BY BOVINE SERUM-PERTUSSIS MIXTURES*

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CLINICALLY it is well recognized that allergic patients are subject to frequent infections of the sinorespiratory apparatus.[1-3] Sinusitis and bronchitis, in particular, have been noted. Less frequently one encounters bronchiectasis and a variety of pneumonitis, sometimes with bronchopulmonary stenosis.[4] Particular vulnerability to the common cold is also observed, although it may be difficult at times to differentiate this type of infection from allergic rhinitis. Most often the enhanced infectibility of the allergic patient is explained on mechanical grounds—increased mucus production, bronchospasm and stasis, and possibly impairment or loss of ciliary function.

That sensitization, per se, may modify the defensive mechanisms of the host has not been previously reported. The following experiments were designed to investigate the possible role that a generalized type of sensitization of the anaphylactic type may have on the infectibility of the host (the mouse) to a standard type of infection with a known strain of staphylococcus.

METHODS AND MATERIALS

Animals.—Two strains of albino mice were utilized in these experiments. One was available from Carworth Farms, New City, New York; the other was the Rockefeller-Swiss strain of the Rockefeller Institute. Female mice, aged 6 to 10 weeks, were selected, as this group was reported to be more susceptible to sensitization. All the animals employed in a given experiment were of the same age and were provided with the same diet and housing.

Antigens.—Bovine serum available in sterile ampule form (Difco) was employed as the antigen throughout the experiment. Rabbit serum and egg albumen were employed only as challenging antigens to determine specificity.

Adjuvants.—Pertussis vaccine was employed as an adjuvant to enhance sensitization to the bovine serum.[5] Two types were used. One, available for human prophylaxis, was supplied through the kindness of Dr. Stanton M. Hardy of the Lederle Laboratories, Pearl River, New York. This contained approximately 60 billion cells per milliliter. The other, used for experimental purposes only, contained approximately 1,000 billion cells per milliliter, and was made available through the courtesy of Dr. J. Munoz of Sharp & Dohme, Glenalden, Pennsylvania. With few exceptions, approximately 12 billion organisms were injected along with the serum.

Injections.—For sensitization, the antigen and adjuvant were given intraperitoneally at the same time. Infective and challenging doses were administered intravenously.

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*Dr. René Dubos of the Rockefeller Institute, New York City, made the facilities of his laboratory available for these studies and participated in their design and execution. These favors are gratefully acknowledged. Technical assistance was given by Miss Jane Buckalew.

Bacterial Cultures.—A coagulase-positive strain of *Staphylococcus aureus* (Smith) was employed. This strain is described elsewhere and its infectibility is well known and predictable in mice.[6] It was used as an 18-hour-old culture in beef heart infusion-peptone broth.

Infectibility.—This was determined by the viable organisms available from organs. The technique is described elsewhere.[6]

Anaphylaxis.—Anaphylaxis, when induced, was either of the mild form manifested by sluggishness, mild dyspnea, and cyanosis of the ears and tails, or was severe and fatal. The severe and fatal anaphylactic reactions usually occurred within thirty to sixty minutes and were manifested by aggravation of the above symptoms, in addition to which were noted wobbling gait, loss of sphincter control, convulsions, paralysis or cycling movements of the legs, and death. In a few instances anaphylactic death occurred several hours after the challenge. No autopsies were performed. The survivors, on recovery, appeared normal in all respects.

The first experiment was designed to (1) demonstrate the induction of anaphylaxis in the mouse by sensitization with beef serum along with pertussis vaccine; (2) demonstrate the specificity of the sensitization; and (3) determine a minimum challenging dose which would not kill the animal and which ultimately could be employed along with the infecting agent in the ensuing experiments. The results are recorded in Table I.

TABLE I. SENSITIZATION OF CARWORTH FARMS MICE TO BEEF SERUM

DAY OF CHALLENGE FOLLOWING SENSITIZATION	CHALLENGING ANTIGEN (ML.)	SURVIVORS	
		SENSITIZED	CONTROLS
		0.05 ML. PERTUSSIS (LEDERLE) 0.5 ML. BOVINE SERUM	0.05 ML. PERTUSSIS
14	0.2 Bovine serum	0/5	5/5
	0.1 Bovine serum	0/5	5/5
	0.05 Bovine serum	2/5	5/5
	0.02 Bovine serum	1/5	—
	0.005 Bovine serum	1/5	—
	0.001 Bovine serum	5/5	—
19	0.001 Bovine serum	2/5	5/5
	0.001 Bovine serum	4/5	—
	0.0005 Bovine serum	5/5	—
	0.2 Rabbit serum	5/5	5/5
	0.01 Rabbit serum	5/5	5/5
	0.2 1% Egg albumen	5/5	—

Eighty-five mice of the Carworth Farms strain were employed. Fifty-five of them were sensitized with the combined pertussis-serum mixture, while the remaining thirty serving as controls were given the pertussis vaccine only. It is apparent here (Table I) that sensitization is of a high order and that, with sufficient antigen, anaphylactic death can readily be induced. The serum, however, when employed in the order of 0.001 or 0.0005 ml. failed to produce death (with one exception) and this was the dose subsequently selected for administration along with the infecting agent. That the sensitization was specific was indicated when challenging doses of either rabbit serum or egg albumen failed to induce anaphylaxis.

In the second sensitization experiment, fifty-five female mice of the Rockefeller-Swiss strain were employed to note any variation of response due to difference in strain. In addition, for control purposes, serum alone without pertussis was employed and found to be sensitizing but to a lesser degree than the combined serum-pertussis vaccine. The results are recorded in Table II.

TABLE II. SENSITIZATION OF ROCKEFELLER-SWISS MICE TO BEEF SERUM

DAY OF CHALLENGE FOLLOWING SENSITIZATION	CHALLENGING ANTIGEN (ML. BOVINE SERUM)	SURVIVORS			
		SENSITIZED		CONTROLS	
		0.05 ML. PERTUSSIS (LEDERLE) 0.5 ML. BOVINE SERUM	0.5 ML. BOVINE SERUM	PERTUSSIS VACCINE (LEDERLE) 0.05 ML.	SALINE 0.5 ML.
21	0.1	0/5	2/5	5/5	5/5
	0.01	0/5	3/5	5/5	5/5
	0.003	3/5	4/5	—	—
	0.001	2/5	—	—	—

For the third experiment, which was designed to investigate the role of prior sensitization upon infectibility, eighty female mice of the Rockefeller-Swiss strain, all 6 weeks old, were employed. These were divided into two equal groups: the first group was sensitized with the bovine serum-pertussis combination, while the second group received only pertussis vaccine. The infecting agent was the "Smith" strain of staphylococcus, previously employed in this laboratory, whose infectibility was well known in mice.[6] The staphylococcus was introduced intravenously simultaneously with the challenging dose of bovine serum (0.001 ml.) previously estimated to produce no anaphylactic death. The challenge and infection were introduced on the tenth, eighteenth, and twenty-third days following initial sensitization. Twenty-four hours later the animals were sacrificed; the organs were emulsified, and from the emulsion loopfuls were streaked on plates and incubated for eighteen to twenty-four hours. This procedure has been employed frequently in this laboratory and the approximate number of colonies available from the organs is known and predictable.[6]

The results of the experiment, as recorded in Table III, definitely indicate the enhancement of infectibility to the staphylococcus by prior sensitization. High colony counts were obtained from the kidney, which is in accord with previous observations,[6, 7] the highest, however, were from the kidneys of the sensitized mice. Furthermore, there is a correlation between degree of sensitization and degree of infectibility. The highest colony counts were noted after the third week following sensitization, when sensitization was at its highest.

In view of recent observations in this laboratory that pertussis vaccine has a protective effect against infection with a variety of agents,[8] it is possible that, with the use of a different adjuvant, the degree of infection might have been even higher. As little as 0.0006 ml. of the pertussis vaccine (Sharp & Dohme) was found to be protective.

The protective as well as the adjuvant action of pertussis vaccine is readily demonstrable in the fourth experiment, in which varying amounts of the vaccine were employed. As in the previous experiments, the sensitizing agent was beef serum. The pertussis vaccine used as the adjuvant was changed to a more concentrated one (Sharp & Dohme). All the challenges

TABLE III. THE EFFECT OF SENSITIZATION ON STAPHYLOCOCCAL INFECTION IN MICE

CHALLENGING AND INFECTIVE DOSE	DAY OF CHALLENGE FOLLOWING SENSITIZATION	ORGAN	NUMBER OF COLONIES CULTURED FROM ORGANS*							
			SENSITIZED				CONTROLS			
			0.5 ML. BOVINE SERUM 0.05 ML. PERTUSSIS (LEDERLE)				0.05 ML. PERTUSSIS			
0.1 ml. staphylococcus ("Smith") 0.001 ml. bovine serum	10	Kidney	4	14	85		0.2	1	12	
		Liver	53	140	148		27	39	103	
		Spleen	53	87	?		12	14	57	
		Lung	13	22	31		0.2	2	57	
	18	Kidney	8	55	160	2900	0.1	1	5	35
		Liver	24	210	310	1100	5	48	56	230
		Spleen	2	2	30	78	8	12	76	101
		Lung	3	6	17	210	0	0	0.4	2
	23	Kidney	560	3200	3500		25	80	750	
		Liver	78	170	300		12	17	47	
		Spleen	30	33	84		4	5	80	
		Lung	0	1	4		0.1	1	1	

*The figures given are to be multiplied by 10^4 for the total colonies available from the kidney, liver, and spleen, and by 10^3 for the lung.

were made on the twenty-sixth day following sensitization. Some deaths (anaphylactic) occurred within four hours after challenge, particularly in those animals treated with higher concentrations of pertussis vaccine. The low number of colonies available in this group from the kidneys and lungs of the infected mice that survived reflects the protective action of the pertussis vaccine (Table IV). Where pertussis was employed in lower concentrations,

TABLE IV. THE EFFECT OF PRIOR SENSITIZATION WITH BOVINE SERUM-PERTUSSIS VACCINE ON INFECTION OF MICE WITH STAPHYLOCOCCI

SENSITIZATION		STAPHYLOCOCCUS INFECTION (0.1 ML. "SMITH" STRAIN IN 0.001 ML. BOVINE SERUM)										
BOVINE SERUM (ML.)	PERTUSSIS VACCINE (ML.)	DEATH WITHIN 4 HOURS	STAPHYLOCOCCUS COLONIES IN ORGANS									
			LUNGS					KIDNEYS				
0.5	0.02	3/5	4	10				2	12			
	0.006	0/5	10	10	10	300	300	1	70	400	1100	3000
	0.0006	1/5	100	240	250	3000		5	100	1700	5000	
	0	0	30	30	30	290	500	11	17	100	300	1200

Note: All challenges were made on the twenty-sixth day following sensitization.

fewer anaphylactic deaths occurred, and higher colony counts were obtained from both lungs and kidneys. In the absence of pertussis vaccine, no anaphylactic deaths occurred and the staphylococcus infection was less severe.

DISCUSSION

The induction of hypersensitivity of the anaphylactic type in the mouse has been difficult in the past.[9] Compared with the guinea pig, sensitization has been sporadic and often variable with the strain employed. Utilizing large volumes of horse serum (4 c.c.), it has been possible to increase the number of mice succumbing to anaphylaxis. This method, introduced by Mayer and Brousseau[10] and subsequently employed by Nelson, Fox, and Freeman,[11] was criticized by Solotorovsky and Winsten[21] because of the profound change in blood volume induced in this fashion. These workers employed alum-precipitated antigen with excellent results. Since the introduction of pertussis vaccine as an adjuvant by Parfentjev and Goodline,[13] however, such sensitization is now readily achievable. Reports on this technique are now available from several laboratories.[5, 14] Utilizing this sensitizing tool along with bovine serum, it was possible to induce anaphylaxis in two strains of mice and to observe the effect of prior sensitization upon infectibility with the staphylococcus.

The role that pertussis inoculation plays in the induction of hypersensitivity when administered along with a specific antigen is not clearly understood. Originally it was thought that the capability of the vaccine to enhance the mouse's susceptibility to histamine was the important factor, assuming that histamine release was involved in anaphylaxis of the mouse.[13] This, however, does not seem to be the case, since the peak of histamine sensitivity is reached on the fourth day following inoculation with the vaccine, whereas hypersensitivity reaches its peak by the third week.[15]

The role that pertussis vaccine plays when injected into the mouse is a complex one.[8] It is an adjuvant, enhancing hypersensitivity to other antigens[5]; it produces simultaneously sensitivity to the nucleoproteins of the vaccine as well as immunity to infections with pertussis[15]; and apparently it modifies the host's resistance to infection with other agents.[16] In the case of gram-negative infections, Parfentjev demonstrated that prior vaccination with pertussis made mice vulnerable to infection with *Pasteurella* and *Bacillus proteus*[16] and to Shigella endotoxin.[17] Observations by Dubos and Schaedler,[8] on the other hand, show pertussis vaccination to exert a protective effect against a variety of organisms, as was demonstrable in these studies with staphylococci. Pertussis vaccination may enhance the susceptibility of mice to infection with influenza virus.[17]

Dubos and Schaedler[8] have shown that the action of pertussis is biphasic, that immediately following injection (up to five hours) infection is enhanced, but thereafter there is an increased resistance to infection lasting as long as six weeks.

Despite the protective role of the pertussis (originally employed only for its usefulness as an adjuvant), the experiments described herein indicate that prior sensitization of mice makes them vulnerable to a standard type of infection with staphylococci. These organisms were selected because standard

techniques were available and the degree of infectibility was predictable. It is possible that other infective agents may exert similar action.

The mechanism by which a general type of sensitization enhances infection is not known. In view of the intimate relationship between allergy and immunity (both are forms of antigen-antibody reactions), it is not surprising that one may affect the other.

Whether these experimental observations truly reflect clinical experience awaits further study.

CONCLUSIONS

Sensitization of two strains of mice by the simultaneous injection of bovine serum and pertussis vaccine made these mice more vulnerable to infection with staphylococci.

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REMOVAL OF A SKIN-REACTIVE COMPONENT IN RAGWEED POLLEN EXTRACT BY HUMAN SERUM PROTEIN PRESENT AS AN IMMUNOLOGIC PRECIPITATE

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IN THIS article the allergenic activity of a fraction of ragweed pollen is shown to be removable by means of a precipitate made by mixing rabbit anti-human-gamma-globulin serum and serum from a patient or subject who had received a series of injections of ragweed pollen extract. The procedure depends on the capacity of antibody to combine with antigen when the antibody itself is present as an insoluble immunologic precipitate. It has been shown by others that rabbit antiequine serum will precipitate soluble equine tetanal antitoxin and that rabbit antiequine serum does not bring about dissociation of diphtheric toxin-antitoxin complexes,[1, 2] nor does precipitated antitoxin lose its antitoxic activity.[3] More recently it was shown that a precipitate made with rabbit antiequine serum and equine antiovalbumin serum would combine with ovalbumin[4] but that in similar experiments equine antihemocyanin serum, presumably because of stearic hindrance, failed to combine with hemocyanin.[5]

MATERIALS AND METHODS

Rabbit antiserum for human gamma globulin was prepared essentially as described elsewhere.[6] Immunologic precipitates were made in most instances by mixing twenty parts of rabbit antiserum and one part of human serum (see below). After standing overnight in an icebox, the precipitates were washed by suspension and centrifugation in three exchanges of chilled saline. The precipitate was then suspended in a finely divided state in a solution of allergenic extract. After thirty minutes, the precipitate was removed by centrifugation and the allergenic activity of the supernatant was assayed in the skin of a suitable subject. A reduction in allergenic activity of the supernatant, as compared with an unabsorbed aliquot of the solution of allergenic extract from which the supernatant was prepared, was considered to be evidence that the allergen had been removed by the precipitate.

The human sera were obtained from unselected normal subjects and from three normal subjects and two ragweed pollen-sensitive patients who had received a series of injections of ragweed pollen extract. All sera obtained from the injected normal subjects and patients had neutralizing activity as determined by titration in passively sensitized skin sites in normal subjects.[7]

Crude allergenic extract was prepared from defatted ragweed pollen extracted with distilled water in a proportion of 1 to 10 by weight. Fraction I[8]

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was prepared essentially as described elsewhere.[9] A precipitate was obtained from crude pollen extract at pH 4 by the addition of ammonium sulfate to saturation. The precipitate was redissolved and again precipitated four successive times. Fraction I was then obtained by precipitation and reprecipitation with ammonium sulfate at 50 per cent saturation, following which the ammonium sulfate was removed by dialysis. The resulting solution was not entirely free of Fraction II as judged by the persistence of some skin reactivity after heating for one hour at 70° C. One unit of Fraction I is defined as 0.00001 mg. of nitrogen precipitable with phosphotungstic acid.

RESULTS

Among twenty-one experiments designed to detect removal of allergenic activity by precipitated serum from normal subjects or from patients who had received a series of injections of crude ragweed pollen extract, evidence for removal was obtained in eighteen. Such evidence was not consistently obtained when the supernatants were made with dilutions of crude pollen extract tested in the skin of patients with ragweed hay fever. However, if such tests were made in the skin of normal persons passively sensitized with serum from pollen-sensitive patients or if Fraction I was substituted for crude pollen extract, the precipitates obtained from 0.1 to 0.5 ml. of human serum consistently removed or markedly diminished the skin reactivity of solutions containing 150 to 1,000 Noon units of crude pollen extract or 2 to 200 units of Fraction I in a volume of 1 ml. Five similar tests done with serum from normal subjects who had received no injections of ragweed pollen extract gave no evidence of removal of allergenic activity, and in a sixth subject equivocal evidence for such removal was obtained (see below).

Within the quantitative limits of the procedures involved, the correlation between the results obtained with the precipitates made with the human sera and the titers obtained by the neutralization tests made in skin with mixtures of human serum and ragweed pollen extract,[7] indicated that the neutralizing or blocking antibody was involved. However, the design of the experiments was not such as to yield results sufficiently quantitative to warrant the conclusion that this antibody alone was involved, a point which will require further study.

An experiment is described in some detail below and in Figs. 1 and 2. In this experiment the supernatants were tested in triplicate in order to minimize error which might be introduced by the variability of reactions obtained with the skin test procedure. It was shown that equivalent and fivefold concentrations of Fraction I, in terms of unabsorbed extract added, exhibited no evidence of allergenic activity and that a concentration twenty times greater gave skin reactions distinctly less intense than those obtained with unabsorbed Fraction I or Fraction I exposed to a resuspended precipitate prepared from serum from a normal person who had received no injections of ragweed pollen extract (Fig. 1). When the concentration of Fraction I, in terms of unabsorbed extract added, was 100 times greater, however, intense skin reactions were again obtained. In this experiment, the concentration of Fraction I, in

which the precipitate was dispersed and subsequently removed, was 1,000 times that required to produce an intense reaction in the skin of the test subject. These results indicated, therefore, that more than 90 per cent of the allergenic activity of the extract had been removed by the precipitate.

SUPERNATANT OR SOLUTION INJECTED			REACTIONS OBTAINED FOLLOWING THE INTRACUTANEOUS INJECTION IN TRIPLICATE OF 0.02 mL. OF SOLUTION OR SUPERNATANT INDICATED ←5 cm.→		
OBTAINED FROM	DILUTION	FRACTION I IN TERMS OF UNABSORBED EXTRACT ADDED U./mL.			
Saline "absorbed" with Precipitate from LOM Serum	UNDILUTED	0			
Fraction I 100 u./mL.	1:1000	0.1			
Fraction I - 100 u./mL., Absorbed with Precipitated: Normal Serum	1:1000	0.1			
LOM Serum	1:1000	0.1			
	1:200	0.5			
	1:50	2			
	1:10	10			
Saline Solution Used in Preparing Supernatants & Dilutions					

Fig. 1.—The inner area (shaded) represents the area and configuration of the wheal, the outer (unshaded) area that of the erythema. Tracings were made by overlaying the test sites with cellophane. All readings were made exactly twelve minutes after injection of the solution to be tested.

The precipitate used in this experiment represented 0.4 ml. of Lom serum. This serum was active in sensitizing normal skin in a dilution of 1:100, required the addition of 750 u of Fraction I per milliliter of serum to prevent sensitization of normal skin, and had a neutralizing capacity (7) lying between 300 and 1,000 Noon units of crude pollen extract.

The same supernatants were also tested in sites in the skin of a normal subject sensitized passively with serum obtained from a patient with ragweed hay fever (Fig. 2). The level of reactivity of the sites was so low as to require the use of undiluted supernatant, and a titration was therefore not attempted. No evidence of allergenic activity was evident in the supernatant obtained after absorption with precipitated serum from the treated patient. The precipitate obtained from serum from a normal subject gave equivocal evidence of absorption as judged by the slightly less intense reactions obtained with this supernatant as compared with the unabsorbed allergenic solution. This was the only

instance in which a precipitate made with serum from a normal subject, who had received no injections of pollen extract, appeared to remove allergenic activity, and its significance is not clear at this time.

A single preliminary experiment along similar lines was carried out with insulin labeled with I^{131} and serum from a diabetic patient highly resistant to insulin. It was shown by paper electrophoresis, using a technique which has

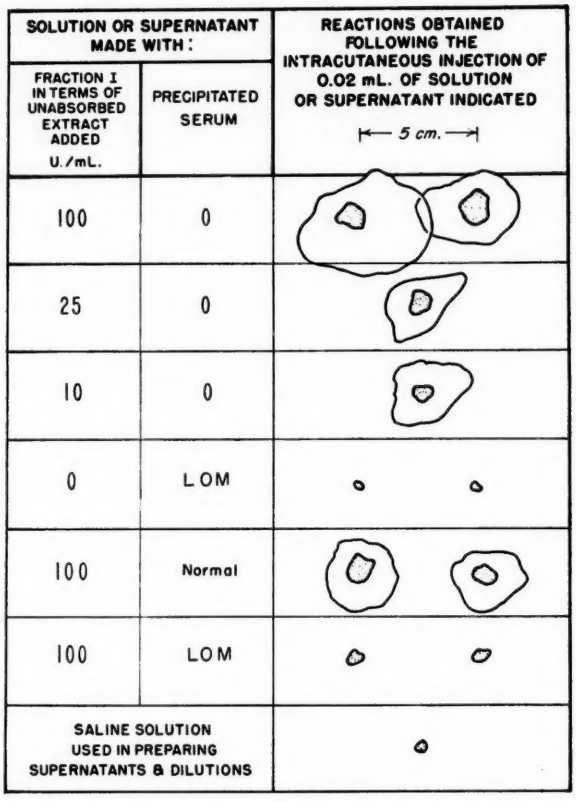

Fig. 2.—For explanation, see legend to Fig. 1.

been described elsewhere,[10] that this serum had the capacity to bind labeled insulin. Absorption of insulin by the precipitate made with the patient's serum was evident, whereas this was not seen when a precipitate made with serum from a normal subject was used as a control. The experiment was complicated by absorption of insulin onto glass surfaces and this interfered with a quantitative estimate of the amount of binding with the precipitate. Although the use of a radioactive tracer is not applicable to such complex mixtures as pollen extracts, it is felt that the precision presumably obtainable with a radioactive tracer, when a single antigen is used, warrants further studies of binding by antibody present as an immunologic precipitate by such means.

DISCUSSION

The results indicate that at least one skin-reactive component in ragweed pollen extract, Fraction I, combines with and may be removed by precipitated antibody derived from the serum of normal persons and patients after they had received a series of injections of crude ragweed pollen extract. Although combination of antibody with antigen under these circumstances has been recognized for many years, we are not aware of attempts to apply this principle to the detection of antibody.

The procedure, though having the disadvantage common to all methods which entail bio-assay (skin testing), has certain advantages in studies designed to detect and perhaps quantitate antibody for allergens (skin-reactive antigens). It appears to be well suited for detection of such allergens, when these are present in immunologically complex mixtures. Since the antibody is present as a virtually insoluble precipitate, there is little likelihood of adding substances to the solution to be injected which would produce nonspecific reactions. Furthermore, tests can be made in the skin of those who are already sensitive and therefore preparation of sites by first injecting serum containing skin-sensitizing antibody is unnecessary.

The nature of the antibody upon which the results depended is in doubt. Since the sera giving positive results were obtained from both normal persons and patients who had received injections of ragweed pollen extract, it is probable that the "neutralizing" or "blocking" antibody was involved, rather than the skin-sensitizing antibody. The failure to obtain positive results in some of the early experiments in which crude extract was used instead of Fraction I suggests that either Fraction II fails to combine with antibody under the circumstances of the experiment or that the persons selected failed to develop antibody for this fraction.

SUMMARY AND CONCLUSIONS

Evidence is presented indicating that combination occurs between a component of ragweed pollen extract and human antibody for this component when the antibody is present as a specific immunologic precipitate. The human antibody involved is presumably "blocking" or "neutralizing" in nature, rather than "skin-sensitizing." The procedure would appear to offer a means of detecting antibody for allergenically active substances in antigenically complex mixtures. Further study will be required in order to determine its suitability for quantitative studies.

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PATCH TESTS WITH THE ETHER-SOLUBLE FRACTIONS OF MOLD PELLICLES

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THE causative role of molds in atopic dermatitis is well known since Feinberg[2] published his studies. However, there is, as far as we can see, no report about contact dermatitis from molds.* Yet, in analogy with ragweed dermatitis, it appears likely that there might also be two forms of dermatitis from molds: (1) atopic dermatitis due to protein fractions of the molds and (2) contact dermatitis due to the ether-soluble oleoresinous fractions. That oleoresins of molds are capable of producing experimental contact dermatitis in animals was shown by Bocobe and associates.[1] The possibility that clinical contact dermatitis might be caused by molds is further suggested by the fact that mold spores and mycelium, like ragweed pollen grains, are known to contain an abundance of oleoresinous material, up to 40 per cent in some species.[5]

For this reason, patch tests with the ether-soluble fractions of mold pellicles were carried out and are reported in this article.

MATERIAL AND METHODS

For these studies, we employed a variety of mold oleoresins which were available as a by-product of our early investigations in the preparation of mold allergens. In these experiments, we had subjected washed, air-dried mold pellicles to extraction in a Soxhlet apparatus with ethyl ether. After removal of all traces of ether by evaporation, the crude oleoresinous substances were dissolved in acetone in a concentration of 1 per cent for patch testing.

TECHNIQUE OF TESTS

The "open patch test" technique was used. Squares were marked with a ball-point pen, and then the individual mold oleoresins were applied; the patch tests were read by the physician during the first three days, and the patient was instructed to check them for four more days.

RESULTS

In 1945, eighty patients were patch tested with the oleoresins of the molds shown in Table I. These patients included especially farmers, persons with contact dermatitis of obscure origin, or those in whom one might suspect contact with molds to be significant. The mold oleoresins were also used in various

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*A contrary note by Grinnell[4] is based on a misunderstanding. Feinberg[2] never observed contact dermatitis from oleoresins of molds.

TABLE I. MOLDS USED FOR PATCH TESTS IN 1945

1. *Alternaria tenuis* (pool)
2. *Alternaria tenuis*
3. *Aspergillus flavus*
4. *Aspergillus niger*
5. *Curvularia trifolii*
6. Fusarium species
7. Helminthosporium (mixed species)
8. *Hormodendrum cladosporioides* group
9. *Monilia sitophila*
10. Sterile mycelium
11. *Penicillium notatum*
12. Penicillium species
13. *Pullularia pullulans*
14. *Rhizopus nigricans* (pool)
15. Spondylocladium species
16. *Trichoderma lignorum*

controls, persons with other dermatoses and respiratory diseases; some of the control group had given positive immediate reactions to a protein extract of alternaria. Contrary to our expectations, all these patients tested were negative.

Between December, 1946, and March, 1949, twenty-five more patients were patch tested with oleoresins from eight molds Nos. 2, 3, 5, 7, 8, 11, and 14 of Table I, plus *Stemphylium botryosum*. All tests again were negative. In November and December of 1955, patch tests were performed on thirty additional patients, using the oleoresins listed in Table II. All the oleoresins except those from *Botrytis cinerea* and *Trichophyton mentagrophytes* had been employed in the earlier tests. All but one of the tests were negative.

TABLE II. MOLDS USED FOR PATCH TESTS IN 1955

1. *Alternaria tenuis*
2. Aspergillus species
3. *Botrytis cinerea*
4. *Curvularia trifolii*
5. Helminthosporium mixed species
6. *Hormodendrum cladosporioides* group
7. Penicillium species
8. *Penicillium chrysogenum*
9. *Rhizopus nigricans*
10. Spondylocladium species
11. *Stemphylium botryosum*
12. *Trichophyton mentagrophytes*

In one patient, helminthosporium oleoresin repeatedly produced a positive patch test consisting of a tuberculin-like reaction with erythema and swelling. After forty-eight hours the lesions became more follicular, but never eczematous and vesicular. This patient suffered from an atopic dermatitis aggravated by house dust sensitivity, and benefited greatly by desensitization with dust. We consider this the first definite positive patch test to mold oleoresin which we have seen. We cannot, at this time, correlate the reaction with the fact that the patient has clinically an atopic rather than a contact dermatitis; nor can we explain the tuberculin type rather than the typical eczematous patch test reaction.

The publication of these reports was delayed because of our reluctance to publish negative results. The number of patients tested was not large enough to permit definite conclusions, except that our extracts were not primary irritants. Our essentially negative results do not exclude molds as a possible cause of contact dermatitis.

SUMMARY AND CONCLUSION

Patch testing with oleoresins prepared from various molds produced only one positive reaction to helminthosporium among 135 patients, many of whom were persons with contact dermatitis of unknown origin where contact with molds was considered a possible cause. This seems to be the first case of a positive reaction to a mold oleoresin in man.

This article is presented in an effort to stimulate others to duplicate the work on a larger scale.

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CLINICAL AND SPIROMETRIC EVALUATION OF ALEVAIRE INHALATION TREATMENT IN PATIENTS WITH CHRONIC ASTHMA

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THE alkyl-aryl polyether alcohol known as Alevaire is a nonionic, relatively inert detergent that acts by lowering surface tension. It can be shown to reduce in vitro the viscosity of mucous secretions and exudates. It is this property which should make Alevaire useful in the treatment of chronic asthma, since obstruction of bronchioles by thickened mucus is one of the main features of the disease.

Alevaire has been extensively investigated by Miller and his co-workers[4-9] as an inhaled aerosol in the treatment of asthma and other pulmonary conditions characterized by mucus obstruction. Their asthma patients were exposed to nebulized Alevaire by means of a tent or nasal catheters, either continuously for several days or for one hour at a time daily. In practically all the cases reported[9] bronchial mucus was liquefied and coughed up, and soon ceased to form. Relief from asthma lasted six to eight months.

In his preliminary report, Frank[2] stated that treatment with Alevaire by aerosol inhalation was of considerable benefit both in acute asthma attacks and in chronic asthma. However, relief did not last over one month and did not seem to depend upon liquefaction of mucus. There were no controls in his study.

Because of negative reports from others using aerosol Alevaire, and because of the lack of controls in previous investigations, we carried out the study reported here. Our purpose was to administer Alevaire and a placebo to patients with chronic asthma, following a modification of Miller's technique, and to evaluate the results objectively by spirometric function tests and clinically by means of a close record of symptoms.

MATERIALS AND METHODS

Thirteen patients from the allergy clinic of the Los Angeles County General Hospital cooperated in this study. Patients were selected on the following basis:

(a) Asthma, continuous for two or more years.

(b) No seasonal variations other than that associated with respiratory infections.

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(c) No notable response to desensitization therapy for one year in patients showing skin-sensitizing antibodies.

(d) Daily production of some mucus from the chest.

(e) Frequent use of expectorants and bronchorelaxing drugs.

There were five men and eight women in the group. Their ages ranged from 18 to 70 years, averaging 56.6 years for the women and 43.4 years for the men. Six patients had a complicating emphysema and one had a concomitant cardiovascular disease. The details of these data are found in Table I, along with data on allergic sensitivity.

TABLE I. SPIROMETRIC RESPONSE TO ISUPREL AEROSOL TEST*

NO.	PATIENT	SEX	AGE	ASSOCIATED PATHOLOGY	ALLERGIC SENSITIVITY	TEST	RESPONSE		PER CENT CHANGE
							INITIAL	FINAL	
1	G. O. M.	M	56	—	Marked pollens; dust	T.V.C.†	2.88	3.26	+ 13.3
						M.B.C.‡	90.5	93.0	+ 2.7
2	G. U. E.	F	59	—	Moderate pollens	T.V.C.	2.22	2.27	+ 2.2
						M.B.C.	48.9	56.9	+ 16.4
3	C. O. N.	F	33	—	Moderate pollens	T.V.C.	2.12	2.22	+ 4.7
						M.B.C.	41.6	31.7	- 23.8
4	L. E. W.	F	42	—	Moderate pollens	T.V.C.			
						M.B.C.			
5	N. E. W.	M	57	Emphysema	None	T.V.C.	1.93	2.63	+ 36.2
						M.B.C.	19.6	39.1	+ 99.4
6	R. A. M.	F	18	Emphysema	Light pollens	T.V.C.	1.28	1.60	+ 17.1
						M.B.C.	26.9	44.	+ 63.5
7	R. O. O.	F	70	Emphysema	None	T.V.C.	1.07	1.12	+ 4.7
						M.B.C.	19.6	19.6	0
8	A. M. A.	F	20	—	Marked dust; slight pollens	T.V.C.	2.84	2.87	+ 1.0
						M.B.C.	87.9	95.3	+ 8.4
9	B. E. L.	M	60	Emphysema	Slight pollens	T.V.C.	1.07	1.28	+ 19.6
						M.B.C.	19.6	29.3	+ 49.4
10	B. A. X.	M	62	Emphysema	Moderate dust	T.V.C.	1.27	.91	- 28.4
						M.B.C.	13.4	19.5	+ 45.5
11	C. H. E.	F	36	—	Moderate pollens; dust	T.V.C.	2.15	2.73	+ 26.9
						M.B.C.	33.2	39.1	+ 17.7
12	D. A. V.	M	48	Emphysema	Moderate pollens; dust	T.V.C.	1.15	1.77	+ 53.9
						M.B.C.	21.5	39.2	+ 82.3
13	F. E. R.	F	69	Cardiovascular disease	Marked dust; moderate pollens	T.V.C.	1.07	1.48	+ 28.9
						M.B.C.	21.5	46.9	+ 118.1

*Isuprel test—six successive inhalations of Isuprel (1-200) aerosol.
†Timed vital capacity in liters.
‡Maximal breathing capacity in liters per minute.

During the period of "base-line" observation and subsequent treatment, each patient kept a daily account of his symptoms and of medications used. Each symptom and use of medication was assigned a value, and at the end of each week of treatment the total value of symptoms and medications was compared to the weekly pretreatment total. This technique, which we have

found useful before,[3] provides a fairly accurate picture of the patients' clinical condition. The clinical estimate was also compared to the patients' spirometric findings to determine any correspondence between the two.

Two forms of apparatus were used to deliver the Alevaire aerosol. The first consisted of a DeVilbiss compressor No. 840 driving a DeVilbiss nebulizer No. 40, which was fed from a reservoir bottle containing 0.125 per cent Alevaire. Half-inch rubber tubing connected the nebulizer to a Hudson-Bennett face mask, held by the patient against his face. A Y-tube bleeder in the compressed-air line allowed for adjustment of the amount of aerosol delivered. Full compressor pressure (approximately 10 P.S.I.) delivered more aerosol than many patients could inhale without suffering from cough and severe dyspnea.

The second method of producing aerosol used the same compressor connected to a Parke-Davis nebulizer which, in turn, was connected to the face mask. This nebulizer delivers less material than the DeVilbiss and was well tolerated by the patients.

Fresh Alevaire solution was used each time. Alevaire is easily contaminated with fungi if exposed to air for a week or two, by which time it has lost some of its ability to liquefy mucus.

The placebo aerosol used consisted of 2 per cent sodium bicarbonate and 5 per cent glycerin in distilled water. This was given to one-half the patients before the study with Alevaire was begun.

Following the work on Alevaire and placebo, one-half of the patients were treated for short periods of time with a mixture of two parts Isuprel (0.5 per cent) and one part Alevaire (0.125 per cent). This mixture was prepared fresh each time and did not discolor during use. The results from this mixture will be presented briefly.

Two methods of aerosol administration were used. By the first method, inhalations lasting approximately one hour were given twice a week for three or more weeks. Twelve patients were treated in this way with Alevaire and six with placebo aerosol. The Isuprel-Alevaire mixture was given to six patients.

The second method of administration more closely resembled that described by Miller. Patients were allowed to take the apparatus home, where they inhaled the Alevaire aerosol for one hour three times a day. Nine patients continued the treatments for three or four weeks. Three others discontinued treatment for various reasons after two, five, and nine days, respectively.

Spirometric measurement of lung function consisted of timed vital capacities (T.V.C.) and maximal breathing capacities (M.B.C.) taken on a Collins 13.5 liter recording spirometer. Patients were checked before any aerosol was given, at one- or two-week intervals during treatment, and in some cases up to four weeks after treatment was discontinued.

Spirometric findings were reported for T.V.C. in liters and for M.B.C. in liters per minute. Since each patient served as his own base line for comparing his own results, the base-line spirometric findings were converted to percentage

of "expected normal" values (Table II) for the purposes of comparing the T.V.C. and M.B.C. of each patient to a common standard. Expected vital capacity was calculated from West's[11] formula:

(a) V.C. (liters) for males = $2.5 \times M^2$ body surface area
(b) V.C. (liters) for females = $2.0 \times M^2$ body surface area

Square meters of body surface area (M^2BSA) was determined for each patient from the monogram prepared by Edwards and Wilson.[1]

Expected normal values of maximal breathing capacity (M.B.C.) was calculated from Motley's[10] formula:

(a) M.B.C. (liters per minute) for males = $(97 - [age/2] \times M^2BSA$
(b) M.B.C. (liters per minute) for females = $(83 - [age/2] \times M^2BSA$

Each patient was tested spirometrically, before therapy of any kind was started, with a standard Isuprel aerosol test consisting of six inhalations of Isuprel 1-200 aerosol orally.

RESULTS

Table I illustrates the spirometric response to the standard Isuprel aerosol test. Of twelve patients tested, eleven showed an increase in T.V.C. ranging from 1 to 53.9 per cent. One showed a decrease of 28.4 per cent. Of twelve patients tested for M.B.C., one showed no change, one showed a decrease of 23.8 per cent, and ten showed an increase ranging from 2.7 to 118.1 per cent. For the most part, the patients with emphysema showed the greatest response, in both T.V.C. and M.B.C., to the Isuprel test. An average response would not be significant, but is reported for comparative purposes. It was 15.0 per cent for T.V.C. and 39.9 per cent for M.B.C.

Some 211 spirometric measurements were made during the present study on thirteen patients. The expected normal values in Table II show that only one patient had either a T.V.C. or M.B.C. value above 70 per cent. Several of the elderly, very ill patients had quite low values, under 30 per cent. However, responses were in no way necessarily related to the patient's original status or to his capacity, therefore, to respond.

Of twelve patients on Alevaire aerosol twice weekly, only four showed a rise in T.V.C., ranging from 8.1 to 30.4 per cent, and averaging 17.7 per cent, while eight showed a decreased response ranging from minus 12.9 to 44.7 per cent and averaging minus 23.9 per cent; the average was minus 10 per cent for the group of twelve (the Isuprel test average was plus 15.0 per cent). Six patients showed a rise in M.B.C., ranging from 8.3 to 55.6 per cent and averaging 18.7 per cent, while six showed a decline in M.B.C. ranging from minus 5.2 to 41.5 per cent, and averaging minus 20.1 per cent (the Isuprel test average was plus 39.9 per cent). There was virtually no correspondence between the spirometric increases in value and clinical improvement.

Clinically, the results depicted here represent the average weekly values during therapy compared to the base-line values.

TABLE II. ACTUAL AND COMPARATIVE SPIROMETRIC RESPONSE TO ALEVAIRE AEROSOL THERAPY

NO.	PATIENT	ASSOCIATED PATHOLOGY	SEX	AGE	TEST	BASE LINE VALUES* (LITERS)	VALUES* AFTER ALEVAIRE AEROSOL THERAPY							
							ALEVAIRE		PLACEBO		ALEVAIRE + ISUPREL		ALEVAIRE	
							TWICE WEEKLY	PER CENT CHANGE	TWICE WEEKLY	PER CENT CHANGE	TWICE WEEKLY	PER CENT CHANGE	3 TIMES DAILY, 3-4 WEEKS	PER CENT CHANGE
1	G. O. M.		M	56	T.V.C.	3.04 (69)†	2.33	- 23.4	—	—	3.23	+ 6.2	3.30	+ 8.5
					M.B.C.	74.2 (61.2)	70.4	- 5.2	—	—	105.6	+ 42.3	93.2	+ 25.6
2	G. U. E.		F	59	T.V.C.	2.38 (62.6)	2.05	- 13.9	—	—	2.10	- 11.8	3.20	- 7.6
					M.B.C.	46.9 (47)	31.3	- 33.3	—	—	31.3	- 33.3	44.4	- 5.4
3	C. O. N.		F	33	T.V.C.	1.28 (38)	1.00	- 21.9	1.00	- 21.9	0.85	- 37.6	1.60	+ 25
					M.B.C.	35.2 (31.7)	54.8	+ 55.6	35.2	0	11.7	- 66.8	48.8	+ 38.6
4	L. E. W.		F	42	T.V.C.	1.48 (44.6)	1.60	+ 8.1	—	—	—	—	1.70	+ 14.8
					M.B.C.	46.9 (45.5)	50.8	+ 8.3	—	—	—	—	40.0	- 14.8
5	N. E. W.	Emphysema	M	57	T.V.C.	1.93 (48)	1.24	- 35.8	1.40	- 27.5	1.07	- 44.6	—	—
					M.B.C.	19.6 (18)	17.6	- 10.2	15.8	- 19.4	15.6	- 21.5	—	—
6	R. A. M.	Emphysema	F	18	T.V.C.	1.79 (81.4)	1.56	- 12.9	1.81	+ 1.1	—	—	1.50	- 16.3
					M.B.C.	39.1 (48)	43.0	+ 22.7	43.0	+ 22.7	—	—	48.8	+ 24.7
7	R. O. D.	Cardiovascular disease	F	70	T.V.C.	0.82 (37.5)	1.07	+ 30.4	0.90	+ 9.7	—	—	1.50	+ 82.9
					M.B.C.	13.6 (19)	11.7	- 14	10.8	- 20.6	—	—	17.8	+ 30.8

*Values in liters: T.V.C. is timed (3 second) vital capacity in liters; M.B.C. is maximal breathing capacity in liters per minute.
†Figures in parentheses are per cent of expected normal values.

†Figures in parentheses are per cent of expected normal values.

8	A. M. A.		F	20	T.V.C.	1.82	(57)	1.58	- 13.2	1.40	- 23.2	—	—	0.87	- 42.2
					M.B.C.	70.5	(61.5)	74.2	+ 5.2	66.8	- 5.3	—	—	52.0	- 26.3
9	B. E. L.		M	60	T.V.C.	1.11	(28.7)	0.83	- 25.3	—	—	0.85	- 23.5	—	—
					M.B.C.	19.6	(19.6)	21.8	+ 11.3	—	—	16.0	- 18.4	—	—
10	B. A. X.		M	62	T.V.C.	1.50	(37.5)	0.83	- 44.7	—	—	—	—	—	—
					M.B.C.	10.2	(10.2)	8.5	- 16.7	—	—	—	—	—	—
11	C. H. E.		F	36	T.V.C.	2.15	(63)	2.38	+ 10.7	—	—	2.55	+ 18.6	—	—
					M.B.C.	56.7	(54.8)	33.2	- 41.5	—	—	58.7	+ 3.5	—	—
12	D. A. V.	Emphysema	M	48	T.V.C.	1.15	(27)	1.4	+ 21.7	—	—	—	—	—	—
					M.B.C.	21.5	(23.8)	23.5	+ 9.3	—	—	—	—	—	—
13	F. E. R.	Cardiovascular disease	F	69	T.V.C.	1.44	(47.2)	—	—	1.08	- 25	—	—	1.40	- 2.8
					M.B.C.	46.9	(62.5)	—	—	35.0	- 25.4	—	—	44.4	- 5.4

Of the six patients given placebo aerosol, four showed clinical improvement of 3 to 30 per cent, and two were worse by 3 per cent and 25 per cent, respectively.

Of the twelve patients given Alevaire twice a week, eight were improved and four were worse, as judged by their clinical scores. Three of these twelve patients (or one-half the total of six on placebo) scored better on placebo than on Alevaire.

The treatments with Isuprel-Alevaire produced short-lived improvement in three of six patients, as would be expected from a powerful bronchodilator. There was no long-term change of significance.

Twelve patients took Alevaire at home. Three discontinued treatment shortly because of increasing asthma. Three more continued for three weeks, but were worse. The decline in clinical score for these six patients who were worse at the end of treatment ranged from minus 15 per cent to minus 56 per cent.

Six patients taking Alevaire daily at home for three weeks or more showed improved clinical scores ranging from 4 to 77 per cent.

The six improved cases were checked for three weeks after the end of therapy. Three had continued to improve, and three were worse again.

Four of the six patients who became worse during treatment had improved during the three-week follow-up period after treatment was discontinued. These results are summarized in Table III.

TABLE III. ALEVAIRE AND PLACEBO INHALATION TREATMENT OF CHRONIC ASTHMA (PER CENT CHANGE AFTER TREATMENT FROM INITIAL CLINICAL STATE)

NO.	PATIENT	SEX	AGE	PLACEBO (PER CENT)	INHALATIONS TWICE WEEKLY			3 TO 4 WEEKS OF INHALATIONS 3 TIMES DAILY, ALEVAIRE (PER CENT)	AVERAGE 3 WEEKS' FOLLOW-UP WITHOUT TREATMENT (PER CENT)
					ALEVAIRE (PER CENT)	ALEVAIRE PLUS ISUPREL	NO. OF ALEVAIRE TREATMENTS		
1	G. O. M.	M	56	—	+ 30	+ 34	16	+ 4	+ 26
2	G. U. E.	F	59	—	+ 20	+ 31	15	+ 65	+ 78
3	C. O. N.	F	33	+ 3	- 2	- 37	9	- 29	- 6
4	L. E. W.	F	42	—	+ 50	—	14	+ 68	+ 37
5	N. E. W.	M	57	+ 17	- 18	- 66	6	- 42	- 35
6	R. A. M.	F	18	- 25	+ 22	—	8	+ 50	+ 20
7	R. O. D.	F	70	+ 32	+ 15	—	10	- 15	+ 36
8	A. M. A.	F	20	+ 19	+ 63	—	9	- 56	0
9	B. E. L.	M	60	—	- 7	- 90	9	- 14	—
10	B. A. X.	M	62	—	- 19	—	10	- 40	—
11	C. H. E.	F	36	—	+ 22	+ 44	7	+ 27	+ 40
12	D. A. V.	M	48	—	+ 20	—	15	—	—
13	F. E. R.	F	69	- 3	—	—	—	+ 77	+ 67
Average change:				+ 7.7%	+ 16.3 %			+ 7.9%	+ 26.3%

When the placebo aerosol was used, 82 per cent of the spirometric tracings showed a decrease in T.V.C. and M.B.C. immediately after use of the placebo. Alevaire treatment was followed by a decrease in these measurements in 85 per cent of the tracings immediately after use of Alevaire. It was apparent that these aerosols have some local irritant property which appears to induce a mild bronchospasm. There was no evidence of increased liquefaction of

secretions which might have reduced the spirometric tests. It was noted that seven patients developed a clinically demonstrable dyspnea from the aerosols when the concentration as delivered through a DeVilbiss nebulizer without benefit of a bleeder (which reduces pressure and concentration) was used. An experiment to determine which factor in the Alevaire preparation was responsible for this action seemed to lay the blame on the concentration of water vapor itself, as the condition was reproduced easily with water alone as the aerosol when the same pressures for delivery were used. Further evidence that the aerosol induced a bronchospasm temporarily was adduced by the fact the patients were capable of recovering their usual levels of T.V.C. and M.B.C. from one week to the next.

DISCUSSION

We have not been able to show any consistent or striking benefit in ambulatory chronic asthmatic patients from Alevaire aerosol inhalations. Eight out of twelve patients were better after inhalations twice a week, but only six of twelve were improved by daily treatment at home. Furthermore, several who improved on treatment at the clinic became worse at home, and vice versa.

Four out of six patients improved on placebo inhalations, which is exactly the same proportion that improved on Alevaire given twice a week. It is true that the percentage of patients who responded to placebo aerosol and Alevaire inhalation was the same, but the mean figures of 18 and 31 per cent, respectively, for the improved patients only are not impressive. The cases who improved at home (one-half) showed a 48.5 per cent improvement. In our studies with several other antiasthmatic drugs, we have come to consider 50 per cent improvement a fair result.

The spirometric measurements of T.V.C. and M.B.C. showed no consistent improvement in any case after administration of Alevaire, either immediately or on the long-range basis of five months' over-all therapy. Since the patients ranged from 10 to 81.4 per cent of predicted normal in these two measures of lung function any consistent improvement should have been detected readily.

The results of this study do not agree with the clinical findings of Miller[9] and of Frank,[2] whose patients were greatly benefited by Alevaire inhalations. Differences in the method of administrating the aerosol would not account entirely for the discrepancy. The giving of inhalations twice a week corresponded to Frank's technique, and those patients we treated for three hours a day compare closely with Miller's patients who were treated at home.

Either our patients did not inhale enough Alevaire to liquefy the mucus responsible for, or contributing to, their symptoms, or else inspissated mucus was not an important cause of their chronic asthma. Probably both explanations have a bearing on our results. Theoretically, to be effective, Alevaire should be inhaled in high concentration for long periods of time for proper

liquefaction of secretions. The relief obtained in any case of asthma would be proportional to the amount of retained secretions in the bronchioles of the patient.

Our results indicate that intermittent inhalations of Alevaire aerosol via a facial mask are of questionable benefit to the average chronic asthma patient. In fact, our spirometric measurements show that such inhalations actually increase temporarily the obstruction to air flow in the lung.

SUMMARY

1. Inhalations of Alevaire aerosol were given to twelve chronic asthma patients twice a week for three or more weeks. Six of these twelve patients also received treatment with a placebo aerosol.

2. Both with Alevaire and with the placebo, two-thirds of the cases improved somewhat in regard to symptoms.

3. Six out of twelve patients treated with Alevaire aerosol for three hours daily for three weeks or more showed some clinical improvement, and six became worse.

4. Pulmonary function as measured by timed vital capacity and maximal breathing capacity did not improve consistently in any of the patients.

5. Intermittent inhalation of Alevaire aerosol does not appear to help the average patient with chronic asthma.

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BRONCHIAL ASTHMA DUE TO SILK

Report of a Case

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INSTANCES of bronchial asthma due to silk sensitization have been reported previously. However, there was no patient in which the sensitivity was proved immunologically and clinically and in whom (1) the only shock organ was the respiratory system and (2) the only sensitization was silk. Such a case of bronchial asthma due to silk sensitization will be reported and discussed in this article.

The raw silk fiber consists of the fibroin cemented together and covered with sericin, in addition to small quantities of wax and coloring matter. Chemically, silk fibroin and silk sericin are proteins. Sericin may be broken down into various amino acids, of which at least twelve have been identified, alanine, tyrosine, glycocol, and leucine being the most abundant. Silk fibroin is a fibrinous material containing predominately glycocol, alanine, and tyrosine, with only traces of leucine.

Meyer and Clarke[2] presented the first report of this condition. It occurred in a 21-year-old woman whose main complaint was urticaria at the point of contact of a silk waist with her skin, in addition to frequent bouts of asthma at night. Intradermal testing with an extract of this silk waist caused a marked skin reaction and an asthmatic attack. This patient also presented positive reactions to extracts of raw silk, "thrown" silk, and silk in the further stages of process. Removal of silk from this patient's environment caused cessation of the asthma, although mild urticaria recurred several times. Asthma and urticaria, in this case, may have been related to the raw silk or to any of the many materials used in the processing of silk, probably as an inhalant sensitivity. This hypothesis was substantiated by the fact that treatment with an extract of the silk waist in question in small amounts was followed by asthma and urticaria.

In 1937 Chiorazzo[3] reported three cases of asthma due to silk waste.

Figley and Parkhurst[4] cited five cases of silk sensitization in association with other atopic manifestations. Asthma was not present in two cases. It was not definitely shown in their case reports that removal of silk cleared the allergic condition or that exposure to silk caused the allergic manifestations.

CASE REPORT

A 6½-year-old girl was first examined on April 15, 1954. She presented a history of rhinorrhea, frequent colds, occasional sneezing, frequent episodes of wheezing, and several

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previous attacks of neurodermatitis, unexplained vomiting, and loss of appetite. The child had a suggestive history of nasal congestion following contact with toilet water, tobacco smoke, and "fluffy" dolls but no apparent reaction to contact with dust. The mother of the child was known to have "rose fever." The patient, under study, had been treated several months previously with dust extract, ragweed, and stock vaccine without any clinical improvement.

Intradermal testing with a group of weak inhalants produced a marked reaction to dust and a very marked reaction to silk extract (raw silk fiber), 100 protein nitrogen units. The silk test (100 PNU) was repeated intradermally to rule out the possibility of error. Five minutes after this second test with silk, the child suffered a marked asthmatic seizure, with cyanosis and dyspnea. Recovery occurred in thirty minutes after two subcutaneous injections of 0.4 c.c. of 1:1000 epinephrine. Pertinent questioning at this time revealed that the child's grandfather was a dealer in cloth remnants and often brought some of these cloth pieces to the patient. Investigation of these remnants showed them to be 20 per cent silk.

By means of the passive transfer test, a marked positive reaction was obtained when the serum site was tested with silk extract, 100 PNU (direct method). Two sites on the other arm of the nonallergic recipient were passively sensitized with the patient's serum. Two days later, the recipient inhaled a small amount of silk powder allergen (indirect method). One-half hour after inhalation of the allergen, the arm sites became red and pruritic, with an absence of edema. The sensitized site on the opposite arm, previously used for an intracutaneous test with silk, itched slightly but showed no redness. Patch tests with silk powder over a site in another recipient and on the patient's skin gave negative reactions.

The patient was advised to avoid silk completely, and therapy with dust, stock vaccine, and silk extract was begun in June, 1954. Treatment with dust extract was included, even though there was no clinical evidence of such sensitization. Mild constitutional reactions of rhinorrhea and cough were obtained when a dose of 1 protein nitrogen unit of silk was reached. There was marked edema at the site of the injection. The patient improved clinically with simple avoidance of silk, but symptoms continued to reappear following repeated injections of silk and persisted for about twenty-four hours after each injection.

Because of the recurrence of symptoms after silk injections, treatment was started in January, 1955, with an alum-precipitated pyridine extract.* Weekly injections of this extract were begun with an initial dose of 0.10 c.c. of a 1:1,000,000 dilution, which was gradually increased. A dilution of 1:10,000 was subsequently reached, and at this point the injections precipitated the same constitutional symptoms previously noted. Consequently, this mode of therapy was also stopped and the patient felt well until June, 1955. At this time the patient wore a dress with a silk collar. Within three to four hours, excessive coughing and sneezing developed. Removal of the offending dress was followed by spontaneous cessation of symptoms in twelve hours. A similar episode occurred several weeks later when the wearing of a silk necktie by the patient's father produced mild nasal and bronchial symptoms in the child. Removal of the silk necktie from the child's immediate environment was again followed by spontaneous disappearance of allergic symptoms.

Silk contact has been carefully avoided in this case and has not been an allergic factor for the past year. The patient has gained considerable weight and has shown great clinical improvement.

DISCUSSION

Treatment of this silk-sensitive patient was unsatisfactory. This result is in accord with our experiences with any "potent" antigen, such as kapok, flaxseed, or horse epithelium. Removal of silk from the patient's environment

*Kindly supplied by Miss Margaret Strauss, made by method described in Strauss, M. B., and Spain, W. C.: Studies on Poison Ivy and Other Dermatitis Producing Plant Parts Wherein Active Resinous Principles Are Suspended in Aqueous Solution, J. ALLERGY **17**: 1, 1946.

in our case apparently caused disappearance of the asthma and desensitization was therefore unnecessary. It has never been definitely proved that desensitization to silk can be successfully accomplished.

Silk waste extract under certain conditions may attain an extensive mold growth. Positive skin reactions to silk waste, as reported by Chiorazzo, could have been due to mold sensitivity. Silk waste is not a specific antigen and can have multiple antigenic variations dependent on the manner in which silk waste is processed.

The cases of silk sensitivity reported in the literature encompass a period from 1923 to 1936. This time interval is well correlated with the peak industrial importation of silk.[5] Inasmuch as the use of silk products is again increasing, it is anticipated that cases of silk sensitization will reappear in the literature and perhaps in the daily practice of the allergist.

CONCLUSIONS

The case of silk sensitivity reported in this article has several unique features.

1. Sensitization in this case has been proved immunologically and clinically by the following diagnostic criteria:

   (a) There was a marked direct skin reaction to silk, 100 protein nitrogen units.
   (b) A constitutional reaction (severe asthma) directly followed the intradermal test for silk.
   (c) Positive passive transfer tests by the direct and indirect methods were obtained.
   (d) Constitutional reactions resulted from treatment with minute doses of silk extract and alum-precipitated pyridine silk extract.
   (e) There was complete disappearance of asthma after removal of silk from the patient's environment.
   (f) Two instances of the return of bronchial symptoms in this patient when silk re-entered her environment were followed by cessation of bronchial symptoms when silk was withdrawn from her environment.
   (g) Patch tests with raw silk fibers on the patient's skin and on a sensitized site were negative.

2. The respiratory system was the only shock organ.
3. Silk was the only sensitization.

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THE ALLERGIST'S STAKE IN COLLAGEN DISEASE

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THE allergist has an important stake in diseases of collagen, as hypersensitivity is thus far the only clue to the etiology of these conditions. In this article, we shall deal with the clinical and experimental proof which supports this view. First, however, in order that this evidence may be better understood we shall present briefly, as essential background information, the anatomy and physiology of connective tissue, the pathology and clinical manifestations of collagen disease, and finally the close interrelationship which exists between these various conditions.

Diseases of collagen are of great clinical importance because of their ever-increasing incidence, puzzling etiology, and serious prognosis. Under this heading are grouped serum disease, periarteritis nodosa, systemic lupus erythematosus (hereafter referred to as SLE), acute rheumatic fever, rheumatoid arthritis, scleroderma, dermatomyositis, and thrombotic thrombocytopenic purpura (TTP). Ulcerative colitis, malignant hypertension, temporal arteritis, and thromboangiitis obliterans, all sometimes considered as collagen disease, for reasons which need not be considered here will not be included in this discussion.

ANATOMY

Connective tissue is found widely distributed throughout the entire body. It is composed of a cellular element (fibroblasts, eosinophils, plasma cells, etc.) and an intercellular substance. When boiled down with water, connective tissue yields a colloidal or collagenous solution of animal glue or gelatin; hence, the name *collagen*. This term has come to be applied to all the extracellular elements of connective tissue, elements which consist of fibers that are held together by a homogeneous amorphous ground or cement substance. The fibers are thought to be derived as follows: The fibroblasts have fine protoplasmic processes which are called fibrils (fibroglia). These run together into heavier fibrils or reticulum fibers. Chemical alteration and/or fusion of these into larger bundles produces the white or collagen fibers. It is apparent that chemical alteration occurs in this process because, while the reticulum fibers take a positive silver stain, the collagen fibers do not. Collagen fibers take an acid stain, such as hematoxylin and eosin, indicating their

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protein or basic nature. Ascorbic acid is apparently essential to the production of collagen.[1] The ground or cement substance is also thought to be secreted by fibroblasts. It is a polymerized carbohydrate-protein complex containing long molecules of hyaluronic acid (an acid mucopolysaccharide) and chondroitin sulfuric acid. The hyaluronic acid predominates where lubrication is necessary, as in joints and in serous cavities, while chondroitin is found particularly where tensile strength is essential, as in cartilage. The ground substance is metachromatic. It also gives a blue stain with Alcian blue, takes colloidal iron, and also Evans blue stain.

PHYSIOLOGY

The ground substance is water binding and holds extracellular fluid. It serves as a medium of exchange of metabolites between the tissue cells and the circulation. This important function is changed as a result of the influence of various noxious agents, so that the long molecules of hyaluronic acid are depolymerized into smaller molecules, thus causing the ground substance to become less gel and more fluid. These nutritional changes in the ground substance inevitably must produce changes in the collagen fibers. Once this occurs, the tissue takes a much redder stain. The source of these alterations is not too clear, but it would seem that they are brought about through the effect of mucolytic enzymes, particularly hyaluronidase.

PATHOLOGY

The following characteristic pathologic changes occur in collagen disease[2-4]: There are swelling, separation, straightening, granulation, fragmentation, and eventual disintegration of the collagen fibers which frequently become argyrophilic. One observes a deposit of swollen, waxy, highly refractile bright red eosinophilic fibrillar material which assumes some of the tinctorial qualities of fibrin; hence, the term *fibrinoid* or *fibrinoid degeneration*. This degenerative process involves not only collagen, but also smooth muscle and ground substance. In all likelihood, fibrinoid is a combination of collagen and mucopolysaccharides. Fibrin also may be found in the tissues at this time. However, it may be differentiated from collagen as follows: Fibrin is digested with trypsin, whereas fibrinoid is not. Upon staining with phosphotungstic acid hematoxylin (P.T.A.H.) after fixation in formalin, fibrin usually stains blue, while fibrinoid takes an orange stain. Fibrin is not as consistently argyrophilic as fibrinoid. Other pathologic findings include necrosis and inflammation with cellular infiltration of lymphocytes, plasma cells, leukocytes, and proliferation of fibroblasts. Eventually repair takes place by replacement fibrosis. These changes are found, to various degrees, in many tissues and organs in collagen disease. The early degenerative stage is usually clinically silent. Signs and symptoms of infection accompany inflammation. Clinical manifestations then develop, depending on the organ affected. It is to be pointed out that, while there is a common pathology, the localization of the lesions varies with each condition.

Necrotizing Angiitis.—Zeek[5, 6] and later others[7-9] proposed a pathologic classification of necrotizing angiitis which has great merit. Our discussion is

concerned particularly with two of the subgroups in this classification, namely, classical periarteritis nodosa and hypersensitivity angiitis.

Periarteritis nodosa (Fig. 1): In classical periarteritis nodosa, originally described by Kusmal, there is involvement of medium-sized arteries with fibrinoid degeneration and hyalinization of the media and perivascular infiltration with mononuclear and polymorphonuclear cells. Intimal proliferation and degeneration lead to thrombosis of the vessels, with or without canalization, ischemia, infarction, and sclerosis. Weakening of the vessel wall may lead to aneurysm formation and hemorrhage. The organs most commonly affected are the kidney, heart, pancreas, adrenals, liver, gastrointestinal tract, muscle, skin, and nerve tissue, but seldom the lung. This disease is

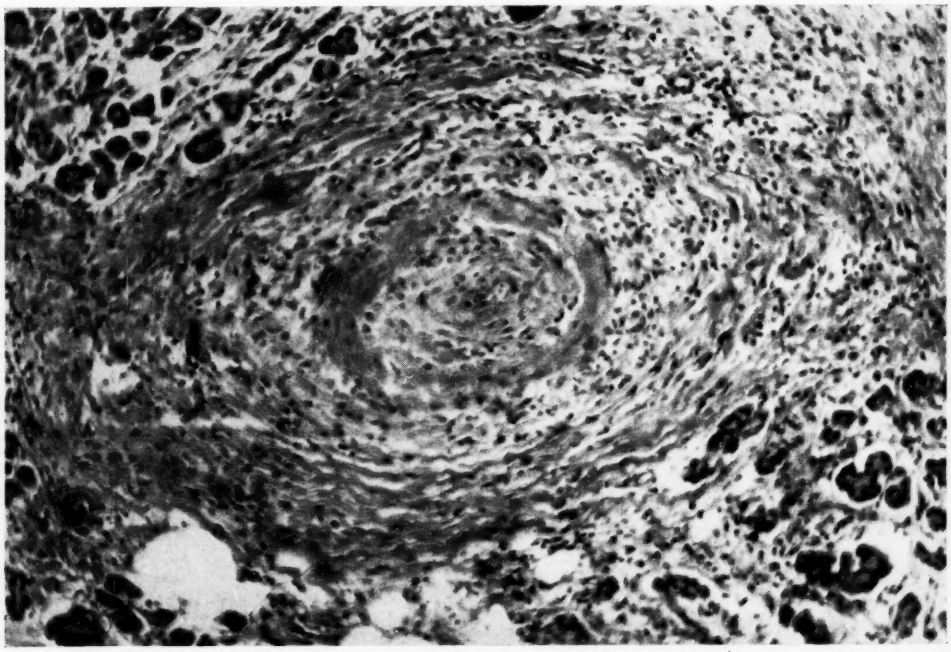

Fig. 1.—Periarteritis nodosa. Blood vessel wall involvement in the pancreas. Note thickening of wall with thrombosis and perivascular infiltration.

usually fatal. Sixteen to 25 per cent of the cases are associated with intractable asthma, urticaria, and high eosinophilia. It occurs primarily in males. It is characterized by prolonged fever, weakness, loss of weight, muscular pains, abdominal symptoms, polyneuritis, enlarged liver, heart and renal failure, microcytic anemia, and tender nodules. In these instances a reversal of the albumin-globulin ratio is found. Steroid administration leads to vascular fibrosis and occlusion. Biopsy makes the diagnosis definite.

Hypersensitivity angiitis: In this condition, on the other hand, there is involvement of the lungs. It is not the medium-sized arteries, but the smallest vessels, that become involved, with the result that organ infarction usually

does not take place. As a rule, there is no disruption of the vessel wall and no aneurysm formation. The disease is iatrogenic (that is, drug induced) and, unlike periarteritis nodosa, it is frequently reversible.

Systemic Lupus Erythematosus (Fig. 2).—SLE is characterized pathologically by changes in the skin, serous membranes, kidney, heart valves, and spleen; the lesion in the kidney is found in the glomerular tufts, where the so-called "wire loop" appearance occurs due to the hyalinization and thickening of the glomerular capillaries and also thickening of the basement membrane. The

Fig. 2.—Systemic lupus erythematosus. Lesions in the kidney involve glomeruli showing endothelial proliferation and "wire loop" lesions.

"onion skin" lesions in the spleen consist of deposition of rings of collagen about the arterioles. The skin is affected because of pathologic changes in the walls of its small arteries. Hematoxylin-staining bodies appear in the tissues of the kidney, lymph nodes, and endocardium.[4] The L. E. cell phenomenon is characteristic. This cell is a mature neutrophilic leukocyte found

in the bone marrow and peripheral blood. It contains phagocyted substances (Hargraves bodies) consisting of degenerated desoxyribose nucleic acid derived from cellular nuclei. The cell is produced by contact with blood plasma because its gamma globulin fraction has a specific protein with antigenic properties. The serum from a patient with SLE may produce this cell when added to leukocytes from normal blood and bone marrow. It is interesting that the signs and symptoms in SLE are far more widespread than the limited pathologic findings would indicate. This suggests the possibility that changes in function may be brought on by immunophysiologic factors other than those represented by the organic pathology. SLE is a constitutional, usually fatal disease which occurs mostly in women and is manifested by long-continued fever, weakness, arthralgia, leukopenia, abdominal pain, "butterfly" erythematous facial skin rash, purpuric lesions of erythema multiforme, pericarditis, pleurisy, endocarditis, anemia, nephritis, retinal changes, adenopathy, splenomegaly, and hepatomegaly. The diagnosis is made by the finding of the L. E. cell.

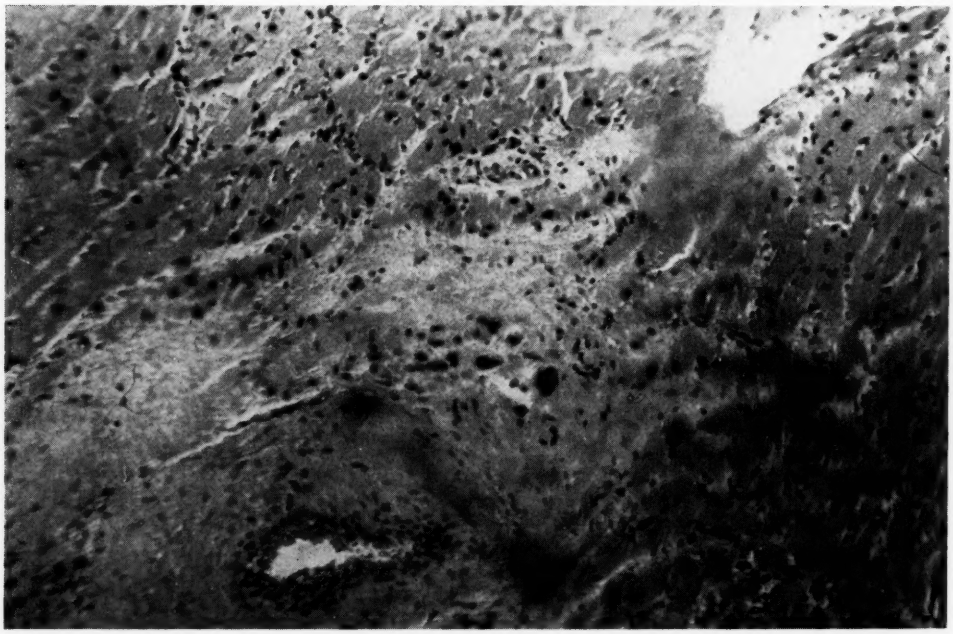

Fig. 3.—Acute rheumatic fever. Myocardial lesions show fibrinoid degeneration, Aschoff body, and replacement fibrosis.

Acute Rheumatic Fever.—In acute rheumatic fever (Fig. 3) we find the Aschoff bodies in the myocardium, the aorta, the lung, and the subcutaneous nodules; there is connective tissue involvement of serous membranes, as well as characteristic inflammatory reaction in the endocardium and coronary arteries. Rarely does pathology occur in the kidney and the spleen. Unlike the lesions of periarteritis nodosa, rheumatic arteritis involves vessels of

smaller caliber; there is no thrombosis and aneurysm formation and the pulmonary vessels may be affected. Clinically, the patient presents evidence of fever and an acute inflammation of successive joints frequently associated with cardiac lesions.

Rheumatoid Arthritis.—Rheumatoid arthritis is characterized by focal degeneration of collagen, a fairly high incidence (less than in rheumatic fever) of cardiac lesions, and less frequently disseminated vascular disease.[10-13] The joints and muscles are affected, leading to a crippling arthritis. Subcutaneous nodules may be present.

Scleroderma.—In scleroderma (Fig. 4) there is deposition of large quantities of collagen in the subcutaneous connective tissue which appears homogenized. The muscle layers, as in the esophagus, are atrophied and replaced with collagen. Fulminating vascular lesions may occur in the kidney.

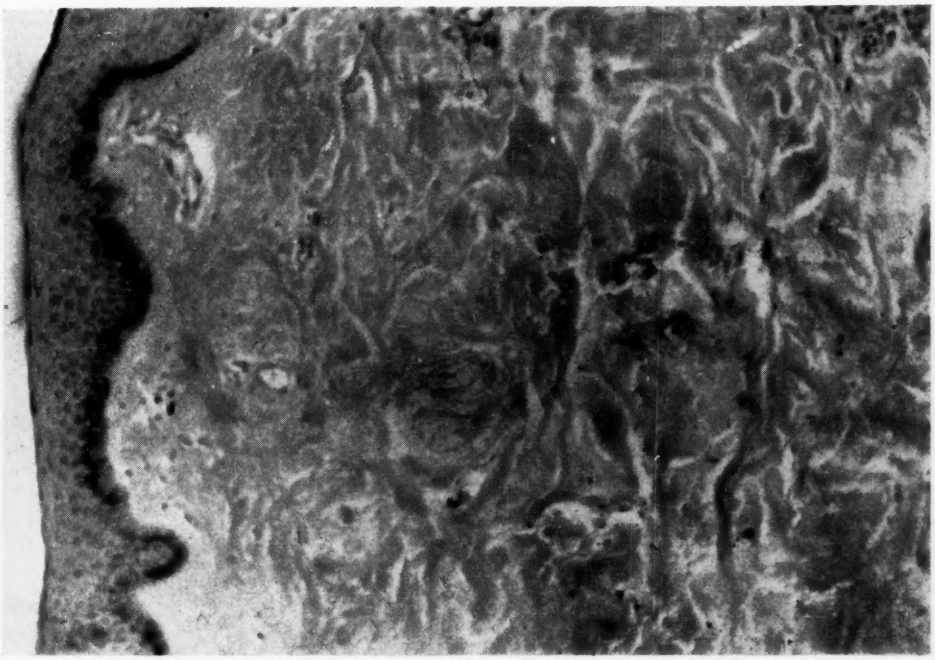

Fig. 4.—Scleroderma. Note increase in and homogeneity of subcutaneous connective tissue with flattening of the papillae of the epidermis.

The patient develops renal infarction, hypertension, and finally uremia. As a result of these changes, there is a diffuse induration and immobility of the skin with pigmentation, sclerodactylia, arthralgia, weakness, weight loss, and occasionally dysphagia, pericarditis, pleurisy, osteoporosis, calcinosis, and renal manifestations.

Dermatomyositis (Fig. 5).—This disease is accompanied by massive increase in connective tissue of the arterial wall with hyaline subintimal proliferation. The blood supply to skeletal muscle is reduced. This, together

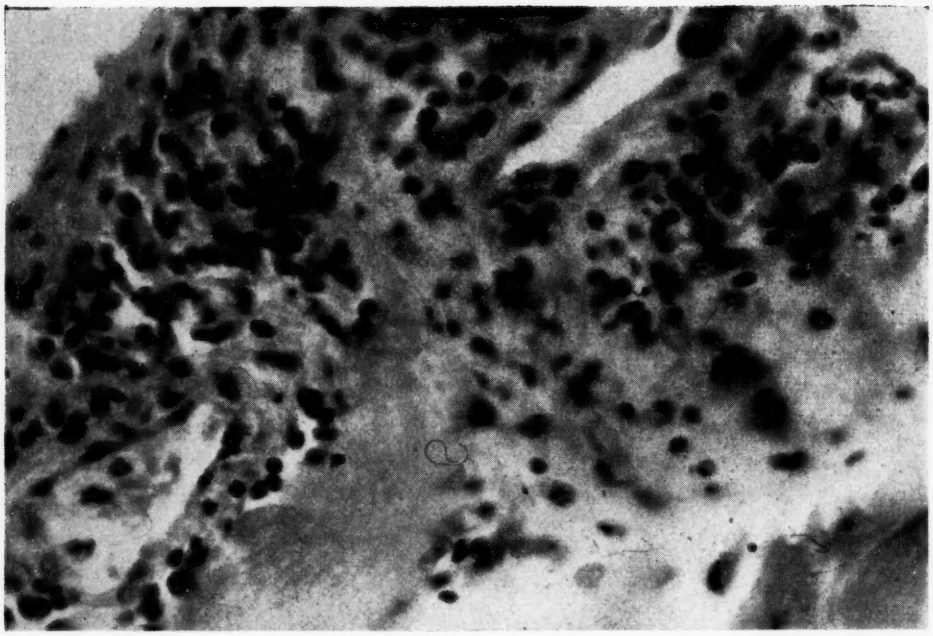

Fig. 5.—Dermatomyositis. Note cellular infiltration and degeneration of muscle fibers.

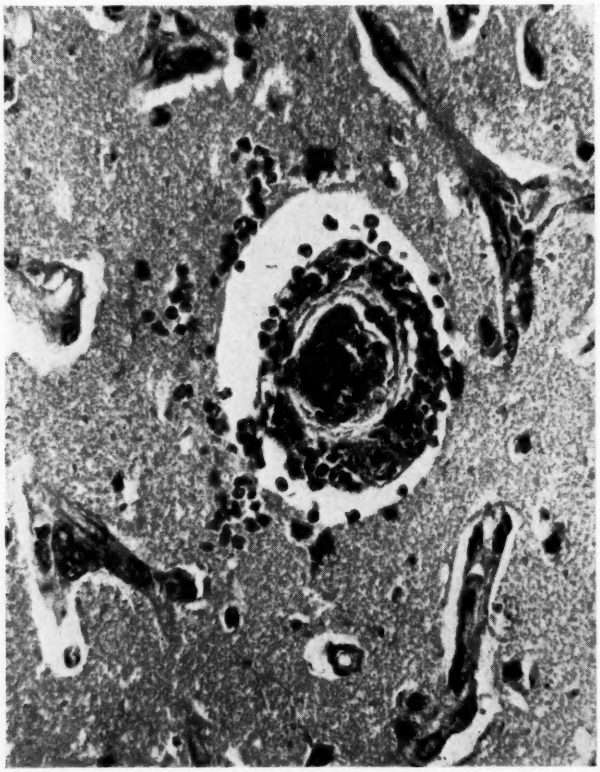

Fig. 6.—Fibrinoid change noted in wall of arteriole containing intraluminal thrombus. Herniation into the perivascular space is also apparent. (Magnification, ×300; reduced ⅓.) (From Fisher, E. R., and Creed, L. D.: **Thrombotic Thrombocytopenic Purpura,** *Am. J. Clin. Path.* **25: June, 1955.)**

with the fibrinoid degeneration of the skin, leads to hyaline and waxy degeneration of muscle with edema and atrophy. Creatinuria is present and is an index of muscular destruction. The disease is fatal. It is characterized by edema, dermatitis, polymyositis, and myasthenia with fever, leukocytosis, albuminuria, occasional eosinophilia, splenomegaly, and contractures due to atrophy and fibrosis of the skin about the joints. Glossitis and diplopia may occur. A muscle biopsy, when positive, is specific for this condition.

Thrombotic Thrombocytopenic Purpura (TTP).—This disease shows primarily a deposit of hyaline acidophilic material in the intima of the terminal arterioles. This pushes the endothelium into the lumen (Fig. 6). As a result of this, it becomes so injured that platelets accumulate on its surface, thus forming a thrombus. Vascular lesions occur in the heart, kidney, and brain, although other organs and systems may be affected, namely, the gastrointestinal tract, pancreas, spleen, and lungs. The condition is characterized by hemolytic anemia, thrombocytopenic purpura, and bizarre neurologic manifestations. Occasionally the disease may be related to drug administration and is associated with eosinophilia, an increase in gamma globulin. The condition is rare, fatal, and difficult to diagnose. It is to be suspected in the presence of thrombocytopenic purpura associated with hemolytic anemia and neurologic findings.

INTERRELATION BETWEEN THESE CONDITIONS

It is evident, therefore, that these diseases have many pathologic and clinical similarities. For this reason, they are easily and frequently confused with each other. Thus, SLE easily may be mistaken for rheumatoid arthritis, rheumatic fever, or periarteritis nodosa. In the case reported by Baggenstoss[14] the patient presented clinically the features of SLE, including even the L. E. cell, but at post-mortem examination the pathology was that of periarteritis nodosa. SLE has also, at times, been mistaken for thrombotic thrombocytopenic purpura (TTP),[15-19] dermatomyositis,[20-23] and scleroderma.[24, 25] Proved instances of periarteritis nodosa have been mistaken for rheumatoid arthritis and SLE.[26-29] Four of fifteen cases of rheumatic heart disease in Spiegel's[30] report were associated with periarteritis nodosa. There are many common clinical findings in rheumatic fever, rheumatoid arthritis, and periarteritis nodosa. Thus, at autopsy instances of acute rheumatic fever showed Aschoff bodies as well as characteristic lesions of periarteritis nodosa.[31, 32] Dermatomyositis may present, early in its course, findings suggestive of acute rheumatic fever[33, 34] or of rheumatoid arthritis.[35] The findings in scleroderma and dermatomyositis may be so similar that some have been led to believe that these two conditions are really one and the same.[16, 33, 36-39, 40-43] Since arthralgia is present in scleroderma, this condition is occasionally confused with rheumatoid arthritis.[44, 45] Similarly other reports indicate the frequency with which there is clinical overlapping in these conditions.[46] This explains why it is frequently virtually impossible to tell clinically whether a given condition is rheumatoid arthritis or rheumatic fever, whether one is dealing with

periarteritis nodosa or SLE, or whether a patient has dermatomyositis or scleroderma. This strong clinical overlapping, as well as the presence of a common pathology, suggests the possibility that diseases of collagen are but various stages or fractions of the spectrum of one and the same disease. Much information on this subject is available in a recent monograph.[47] What is the evidence as to the probable role played by hypersensitivity in the etiology of collagen disease? There are both clinical and experimental data in this connection.

CLINICAL EVIDENCE

Rackemann[48] reports a fairly high incidence of periarteritis nodosa occurring one to twenty-four years after the onset of bronchial asthma. These patients usually present a very high eosinophilia, and their asthma is intractable. The relationship of bronchial asthma to periarteritis nodosa is also indicated by others.[49] Gruber[50] suggested, as early as 1925, that there is an allergic basis for periarteritis nodosa because of its association with urticaria, eosinophilia, and asthma and its artificial production in animals. Since then, there have appeared numerous contributions linking various substances as antigens in the production of periarteritis nodosa. These include penicillin,[51, 52] dilantin,[53] arsenicals,[54] thiouracil,[54-57] foreign serum,[58] iodine,[59] trichina,[60] sulfonamides,[58, 61-64] mercurials,[65] and poison oak.[66] There is, of course, a close relationship between serum disease and periarteritis nodosa. As a matter of fact, periarteritis nodosa occasionally develops in the course of serum disease when its manifestations become visceral and are no longer reversible.[64, 67] Many other observations indicate the relationship of this disease to bacterial hypersensitivity.[48, 68, 69] It would not be unreasonable to suspect that the increased incidence of periarteritis nodosa is real and is due at least in part to the increased use of antibiotics and sulfonamides.[70, 71] Rheumatic fever is occasionally accompanied by such allergic findings as eosinophilia and urticaria. The administration of hydralazine (Apresoline) is known to cause arthralgia and rheumatic manifestations with fever. This drug may produce other manifestations of collagen disease.[72] The fluid obtained from the joints in these cases is sterile. Many years ago, Swift[73] and others[74, 75] established that infections of the upper respiratory tract with nonhemolytic streptococci preceded by a variable time interval typical acute rheumatic fever. It is speculated that the antigen may be an autoantigen activated by the streptococcus.[76] Rheumatoid arthritis also has been related by many as a possible form of delayed bacterial hypersensitiveness. It has been indicated previously that SLE occurs in penicillin-sensitive persons. Hydralazine employed in the treatment of hypertension has produced the manifestations of SLE,[72, 77] including the presence of the L. E. cell and increased serum globulin changes, which disappeaar once the drug is withdrawn. One also finds SLE patients demonstrating both photosensitivity and allergy to cold.[78] Bacterial hypersensitivity, as well as sensitivity to drugs, sera, and vaccines has been frequently related to SLE[79-85] and to periarteritis nodosa, especially with reference to the association of the latter condition and scarlet fever.[86]

Other reports deal with the relationship of joint pains to streptococcus toxin,[87, 88] the occurrence of SLE in student nurses,[89] brain changes in postscarlatinal encephalitis,[90] and the relationship of postscarlatinal arthritis and carditis to rheumatic fever.[91] There is no clinical evidence of an allergic background for scleroderma. In dermatomyositis, sensitivity to sunlight is sometimes a factor,[92] and occasionally this condition is associated with penicillin sensitivity. There are some reports which indicate a possible relationship of thrombotic thrombocytopenic purpura (TTP) to allergy to sulfonamides,[93, 94, 95] to penicillin,[95] infection,[96] and iodine.[97] Antibodies against red blood cells and platelets have not been actually demonstrated and yet all the evidence seems to indicate that these disturbances are mediated by an immune mechanism.

EXPERIMENTAL EVIDENCE

There is very little doubt, of course, that serum disease is mediated by an immunologic mechanism. In this condition as antigen disappears from the circulation, antibody appears. The clinical manifestations of serum disease occur after an incubation period which allows time for antibodies to form, and are due to antigen-antibody union. Germuth[98] has correlated the histologic and immunologic findings in the experimental animal. He indicates that the vascular lesions begin to show at the time when there is a sharp fall in serum antigen concentration and are most marked when there is neither antigen nor antibody excess in the serum; they disappear as serum antibody is increased. This indicates that the lesions develop at about the time when there is antigen-antibody union. Clark and Kaplan[67] describe pathologic lesions similar to those of rheumatic fever in anaphylaxis and serum disease in man. As early as 1923, Gerlach[99] demonstrated that fibrinoid degeneration is found in local anaphylactic lesions, as in the Arthus phenomenon. Rich[100] reports later on similar findings. Masugi and associates[101, 102] produced periarteritis nodosa-like lesions in sensitized animals with the intravenous injection of egg white. Rich and Gregory[103] achieved similar results by the injection of massive doses of horse serum into rabbits. The injection of egg white in mice yielded pathologic changes of rheumatic carditis.[104, 105] Cavelti[106, 107] obtained the changes of rheumatic myocarditis in rats by sensitizing them with an antigen consisting of whole killed hemolytic streptococci and aqueous extract of rat myocardium. In view of this experimental work, it is suggested[108] that acute rheumatic fever pathology may be brought about by the antigenic action of a combination of the hemolytic streptococcus and proteins derived from the damaged myocardium. Likewise, it seems that the injection of viruses produces similar lesions in rabbits.[109] As early as 1929 to 1931, Klinge[110, 111] produced collagen degeneration and necrotizing arthritis by injection of horse serum into the joints of sensitized rabbits. Rich[103] comments on the similarity between the lesions in the experimental animal and those of periarteritis nodosa and rheumatic fever in man and the Arthus phenomenon in the anaphylactic rabbit. Comens[112] fed hydralazine to dogs and induced in these animals the clinical manifestations of SLE as well as L. E.

cells, hematoxylin bodies, and the pathologic lesions in the kidney characteristic of SLE. It should be pointed out, however, that in addition to specific agents, as indicated above, other factors may be responsible for the development of fibrinoid degeneration. These are: wrapping the kidney in cellophane,[113] the administration of desoxycorticosterone,[114] dietary factors,[115] exposure to stress and strain, aging, cold, starvation, and radium, also in various acute bacterial infections, acute pancreatic necrosis, and peptic ulcer. An additional link in the experimental evidence as to the role of hypersensitivity in producing collagen disease is offered by the fact that antihistaminics will prevent the development of horse-serum-induced myocarditis (resembling rheumatic carditis), an effect similar to that exerted by antihistaminics in protecting animals against anaphylactic shock.[116] It is also of interest that, clinically, collagen disease is associated with many immunologic phenomena. Thus, precipitins may be found in periarteritis nodosa. As a matter of fact, it is thought that the lesions in this condition are initiated by the precipitate which forms in the tissues as a result of antigen-antibody union. Heterophilic antibodies may be found in SLE,[117] as they are also found in serum disease. Reiner[118] has shown an increase in the gamma globulin fraction of the serum in SLE. This condition is commonly associated with a positive serologic anticomplementary test for syphilis.[119] Harvey and associates[120] and Teilum[121] suggest that the hyperglobulinemia, periarterial fibrosis of the spleen, and the "wire loop" lesions in the kidney in SLE are indicative of an allergic "hyperglobulinosis" of the reticuloendothelial system. Rheumatic fever is associated with a high-titer serum, antistreptolysin O. One may find in rheumatic arthritis a positive agglutination test to *Streptococcus hemolyticus* as well as hyperglobulinemia. With remission in this disease the hyperglobulinemia disappears. Therefore, it appears that in many of these diseases there is an increase in alpha and gamma globulin and a depression of serum albumin, as well as a rise in fibrinogen and glycoprotein. There is evidence that the gamma globulins are localized in the vascular lesions of periarteritis nodosa in man.[122] Furthermore, more recent data or information[123] indicate that "studies of lesions of rheumatic fever, systemic lupus erythematosus and to a lesser degree rheumatoid arthritis showed significant concentrations of gamma globulin" with lower values for serum albumin. The findings, it is concluded, "are consistent but not specific for the presence of an antigen-antibody reaction in tissue lesions." Experiments conducted by us in conjunction with others, and still in progress, add further weight to the assumption as to the possibility that hypersensitivity plays an important role in the conditions under consideration. We shall briefly enumerate our findings:

1. We[124] demonstrated that total body x-radiation of twenty-eight rabbits (600 r and 800 r of x-ray radiation) twenty-four to seventy-two hours before sensitization with horse serum brings about a marked reduction in the number and intensity of vascular lesions and carditis. This indicates an inhibitory action of x-ray on the development of the lesions. X-radiation of normal nonsensitized animals showed no lesions of diffuse vascular disease. Previous

investigators[125-132] have shown that x-ray exerts a definite depressant effect upon antibody production. Dammin and Bukantz[133, 135] and others[130-132, 134, 136] noted an inhibition of the production of the Arthus phenomenon and the diffuse vascular lesions of hypersensitivity by the use of nitrogen mustard.

2. Bacteria and bacterial products have been implicated in connection with the etiology of rheumatic fever, rheumatoid arthritis, and occasionally SLE. For this reason, we[137] were successful in demonstrating the vascular lesions of experimental hypersensitivity by sensitizing a series of rabbits with streptococcus toxin. This would seem to be significant in light of the report that postscarlatinal myocarditis results from sensitization to the streptococcus and resembles rheumatic myocarditis.[138]

3. In our experiments,[139] we found that sera obtained from rabbits fourteen days after sensitization with bovine plasma albumin showed a high percentage of vascular lesions and gave patterns characterized by an increase in gamma globulin and decreases in albumin and alpha globulin (Fig. 7). These results bear a strong similarity to those obtained by Reiner[118] in human beings suffering from SLE.

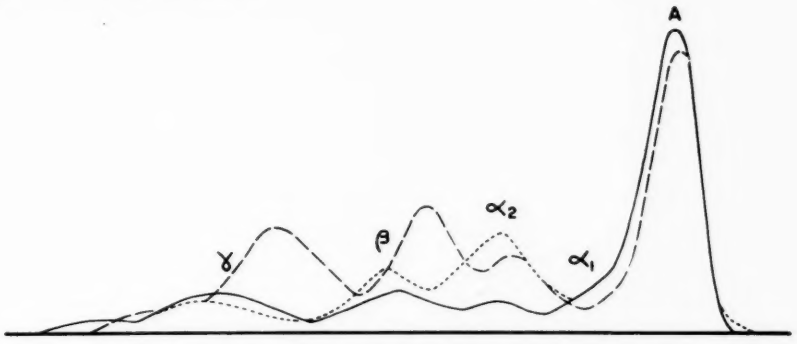

Fig. 7.—Electrophoretic pattern in normal (solid line), sensitized (broken line), and sensitized and cortisone-treated animals (dotted line).

4. We have demonstrated that vascular lesions in experimental hypersensitiveness, as well as the hyperglobulinemia thus induced, are prevented by cortisone[118, 140] and the results are similar to those reported by others.[141]

5. Adrenalectomy, in our experience, enhances the immunologic reactions of hypersensitiveness, just as it enhances anaphylaxis, the precipitin titer, and the severity of the Arthus phenomenon.[142]

6. To indicate further the possible immunologic character of the vascular lesions of hypersensitivity, we demonstrated, in conjunction with Cohen,[143] that these vascular lesions may well be induced in normal recipients (rabbits) by passive sensitization. By this technique, one could eliminate the possibility that the pathologic changes are induced, as has been supposed,[144-149] by the toxic or nonspecific action accompanying administration of large doses of foreign serum.

SUMMARY

Diseases of collagen have a common pathology and common clinical manifestations, and present a marked tendency toward overlapping. They are not infrequently produced by drugs. They respond to steroid therapy. Both clinically and experimentally, they are associated with hyperglobulinemia. They are reproduced experimentally by both active and passive sensitization. The development of these lesions is interfered with by x-radiation and nitrogen mustard. This considerable body of evidence certainly suggests strongly the possibility of a hypersensitivity etiological factor. The allergist is interested in and concerned with phenomena of hypersensitivity. His continued preoccupation with this subject, we hope, will throw additional and much needed light upon this provocative and baffling subject.

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THE USE OF THE THREE-SECOND VITAL CAPACITY IN THE DIRECT TESTING OF BRONCHIAL ALLERGY

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INVESTIGATION of the etiology of a case of bronchial asthma still provides a challenging problem. At present a detailed history with appropriate skin tests is the most reliable means of establishing the etiology. However, it is common experience that while the history may implicate a particular antigen, the skin test with the same antigen may be negative. Conversely, positive skin tests may be obtained to substances clearly unrelated to the history of the patient's illness. Herxheimer[1] recently re-evaluated the use of skin tests in twenty-one patients and found that in only three patients did repeated skin tests give identical results. There is, therefore, some justification for criticism of the value of skin tests in establishing the etiology of a case of allergic asthma.

Several studies of direct bronchial testing in asthmatic persons have already been reported. Stevens[2] made the first such study in 1934, by using a very simple technique in which the test antigen was instilled directly into the trachea. If an attack of asthma developed, then the test was considered positive. Of 158 asthmatic persons whom he investigated, positive bronchial tests were obtained in twenty-three. He did not find any correlation between the intensity of the reaction from a positive skin test and the incidence of positive bronchial tests. Harris,[3] using a somewhat similar technique, tested twelve patients and produced an immediate reaction in eight patients and a delayed reaction in two additional patients. Subsequently a more refined technique was developed in which the test antigen was given as an aerosol. If inhalation of the aerosol resulted in reduction of the vital capacity by 10 per cent, or 600 c.c., the test was regarded as positive. Lowell and Schiller[4] used this method in ten patients, with positive results in seven. They later reported the results of testing seventy-five patients, of whom fifty-seven gave a positive bronchial test reaction.[6] It is of considerable interest that on no occasion were they able to induce a positive bronchial test unless the skin test for that particular antigen was also positive. On several occasions positive skin tests were obtained which corroborated the history and yet the bronchial test was negative. Herxheimer[1] has studied this problem extensively and he reported the results of direct bronchial tests in seventy-one allergic patients. In forty-six of these patients the skin test and the bronchial test were both positive. Fifteen had a positive skin test but a negative bronchial test, while ten had a

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negative skin test with a positive bronchial test. Of these seventy-one patients, there was good correlation between the skin test and the bronchial test in forty-six, but in the remaining twenty-five patients there was considerable discrepancy between the results of the two methods of testing.

It is apparent that a more sensitive direct bronchial test needs to be developed before the skin test can be replaced for the identification of the offending antigen in bronchial asthma. For this reason, consideration was given to the use of the three-second vital capacity as a method of detecting mild bronchospasm or airway obstruction. The patient with bronchial obstruction, such as occurs in asthma or diffuse obstructive emphysema, may have a normal vital capacity but the three-second vital capacity will always be reduced.

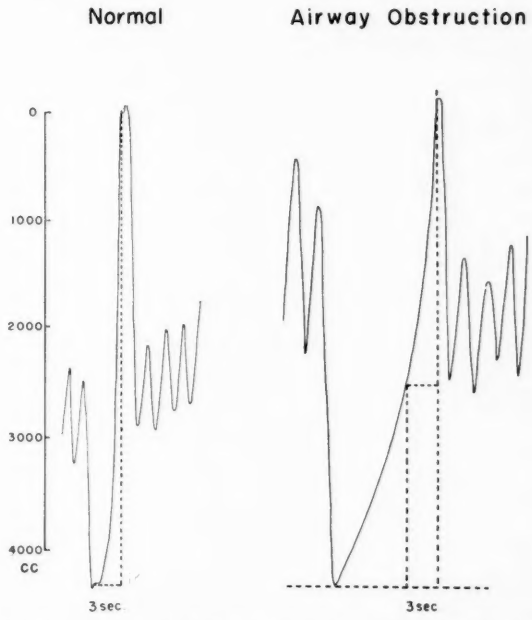

Fig. 1.—Total and three-second vital capacity in a normal patient and in a patient with diffuse airway obstruction.

This is illustrated in Fig. 1. The spirogram tracing in the normal person shows that 97 per cent of the total vital capacity is expired in three seconds, whereas in the patient with airway obstruction the three-second vital capacity is markedly reduced although the total vital capacity remains normal. The difference is due to the bronchial obstruction which prevents rapid expiration but, given sufficient time, these patients are able to produce a normal total vital capacity. As the bronchial obstruction increases in severity, then the total as well as the timed vital capacity will decrease.

It was therefore postulated that if inhalation of a nebulized antigen induced bronchospasm, this change would be elicited at an earlier stage by use of the three-second or timed vital capacity.

METHOD

Patients with a history strongly suggestive of ragweed sensitivity were selected for the study. Altogether seventeen patients were selected, of whom eleven were men and six women, their ages ranging from 22 to 69 years. All were white. These patients were divided into three groups:

Group I: Bronchial asthma, skin test positive to ragweed—4 patients.

Group II: Bronchial asthma, skin test negative to ragweed—10 patients.

Group III: Vasomotor rhinitis, skin test positive to ragweed—3 patients.

The skin tests were done intradermally and carried to a dilution of 1:500. The same ragweed antigen was used for the bronchial tests, all of which were performed in the winter months when the patients were symptom free.

An aerosol of ragweed solution was produced by a Vaponephrin nebulizer attached to a compressed air reservoir. This was so arranged that nebulization took place only during inspiration. At the start of the test, the patient performed a total and a three-second vital capacity, both of which were repeated until values which checked within 100 c.c. were obtained. Next, 0.5 c.c. of 1:100,000 ragweed antigen was nebulized and inhaled by the patient taking near-vital-capacity breaths until the solution was completely nebulized. After a five-minute rest, the vital capacity and timed vital capacity were repeated. If these values were unchanged, then 0.5 c.c. of 1:10,000 ragweed antigen was placed in the nebulizer and the procedure was repeated. As long as no change was obtained in the vital capacity or timed vital capacity, increasingly strong ragweed solutions were used through 1:5,000, 1:1,000, and 1:500 to 1:50. An additional 0.5 c.c. of this last solution was given if no reaction had occurred.

Those patients who had no change in vital capacity or timed vital capacity would receive a total of 3.5 c.c. of ragweed antigen over a two-hour period. It is recognized that an unknown proportion of the antigen would not reach the smaller bronchioles, so that the total effective dose was less than 3.5 c.c.

TABLE I. THE RESULTS OF DIRECT BRONCHIAL TESTING WITH RAGWEED ANTIGEN IN PATIENTS WITH A HISTORY POSITIVE FOR RAGWEED SENSITIVITY

GROUP	NUMBER	POSITIVE BRONCHIAL TEST
I	4	4
II	10	1
III	3	1

RESULTS

Seventeen patients were tested and six positive tests were obtained. There were no delayed positive reactions.

Reference to Table I shows that in Group I (bronchial asthma with history and skin test positive for ragweed) all four patients gave a positive bronchial test. In Group II (bronchial asthma with a positive history for ragweed sensitivity but a negative skin test) one positive bronchial test was obtained. In Group III (ragweed vasomotor rhinitis with a positive skin test) one positive test occurred. This patient had not previously had an asthmatic attack but has the potential to do so, as shown by this test.

TABLE II. THE REDUCTION IN VOLUME OF THE VITAL CAPACITY AND THREE-SECOND VITAL CAPACITY OBTAINED IN THE POSITIVE BRONCHIAL TESTS

PATIENT	RAGWEED SOLUTION GIVING POSITIVE TEST	REDUCTION IN VITAL CAPACITY (C.C.)	REDUCTION IN THREE-SECOND VITAL CAPACITY (C.C.)
R.	1:500	2,200 (50%)	1,500 (50%)
B.	1:5,000	800 (23%)	1,200 (35%)
K.	1:50	Not recorded	600 (13%)
E.	1:500	800 (19%)	550 (17%)
N.	1:5,000	600 (20%)	600 (20%)
S.	1:500	2,200 (51%)	1,300 (52%)

Reference to the results in Table II makes it apparent that the use of the three-second vital capacity did not add any greater sensitivity to the test. Those patients who had a positive test gave no warning before passing from normal to an asthmatic attack, with reduction in the total and three-second vital capacity developing simultaneously.

DISCUSSION

Feinberg and associates[5] have shown that there is a definite variability in organ sensitivity to ragweed. They found that patients with vasomotor rhinitis would tolerate a high concentration of ragweed solution in the bronchi while reacting vigorously to a weak solution in the nose. The reverse was shown in asthmatic patients. As the shock organ in asthma is the bronchial tree, it would be expected to show greater sensitivity than the skin. Yet the skin has proved almost as reliable as direct bronchial testing, both in this and in other series.[4, 6] In this experiment only one positive bronchial test was obtained in ten patients with negative skin tests. Lowell and Schiller were unable to obtain any positive bronchial tests in the presence of a negative skin test, whereas Herxheimer did succeed in obtaining several positive bronchial tests in this situation. Perhaps the explanation lies in the technique which Herxheimer used, with administration of a high concentration of antigen continuously for up to three minutes which may have produced bronchospasm as a result of direct irritation rather than a true allergic response.

There are other factors which may explain the inability of direct bronchial tests to yield more positive results. Acute exposure to the antigen, as occurs in bronchial testing, is unnatural. In normal circumstances, ragweed pollen is inhaled over the course of several weeks, during which time a constant stimulus probably is being given. Furthermore, asthma frequently is due to a combination of antigens. This was well demonstrated by Lowell and

Schiller in a group of thirty patients with a positive reaction to nebulized house dust in whom, clinically, the majority had an exacerbation of symptoms only during late fall when ragweed pollen was at its height.

It is somewhat surprising that the timed vital capacity adds nothing to the sensitivity of the test. Once sufficient antigen has been inhaled to initiate an attack of asthma, the degree of bronchospasm resulting reduces both the total and the timed vital capacities simultaneously. This would indicate that in an asthmatic attack the bronchi do not gradually decrease in diameter, but suddenly pass from a normal to a markedly reduced caliber.

SUMMARY

The use of direct bronchial tests in the investigation of the allergic etiology of bronchial asthma is discussed. It is suggested that the three-second vital capacity would be a more sensitive index of a positive test than change in the total vital capacity.

Seventeen allergic patients were investigated and six positive bronchial tests were obtained. In ten asthmatic patients with a history strongly suggestive of ragweed sensitivity but a negative skin test to ragweed, only one positive bronchial test reaction to ragweed was obtained.

It is concluded that the three-second vital capacity does not increase the sensitivity of the test and that direct bronchial testing does not give sufficient additional information to replace the skin test in the routine investigation of a case of allergic asthma.

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URTICARIA ASSOCIATED WITH GIARDIASIS LAMBLIA

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THE cited causes for acute and chronic urticaria are innumerable. Among them are parasites, mentioned by Sulzberger,[1] who cites cases of ascariasis, oxyuriasis, tapeworm infestations associated with urticaria, and eosinophilia. Sheldon and Mathews[2] mention parasites as possible causes without going into specific detail. After a search of the available literature, I have been able to find nothing associating giardiasis with acute or chronic urticaria.

CASE REPORTS

CASE 1.—A 42-year-old white man complained of severe generalized urticaria of the abdomen, chest, back, extremities, and face for seven days. Accompanying this was severe pruritus, especially of the palms. There was no history of any recent medications, including laxatives, contraceptives, aspirin, or vitamins; there had been no intake of known urticariogenic foods, no episodes of chills and fever, and no obvious significant emotional upsets. No new clothing had been worn recently, and there was no etiological clue other than the presence of mild intermittent "diarrhea" for the past nine or ten years. The number of stools was six or seven per day. There was no blood or mucus associated with these bowel movements; there had been no weight loss, and no change of occupation or place of residence.

Physical examination on repeated occasions showed typical urticarial wheals on all parts of the body, chiefly on the area covered by the patient's clothes. The lesions appeared round or oval, and were between 2 and 5 cm. in diameter. There was generalized hyperemia associated with severe pruritus. The remainder of the examination was not remarkable.

Laboratory examinations were noncontributory, except for a sedimentation rate of 26 and the absence of eosinophilia. Intradermal skin tests were not helpful, as they gave weak reactions to a few foods which did not correlate with the clinical picture. A stool specimen was loaded with *Giardia lamblia* cysts.

Course of Treatment.—The patient was treated with 100 mg. tripelennamine hydrochloride (Pyribenzamine) four times daily for five days. No improvement was observed. The patient was then given 100 mg. diphenhydramine hydrochloride (Benadryl) four times daily for a further 5 days. Again no relief was obtained. The patient was then given prednisolone (Delta-Cortef), 5 mg. four times daily for a third five-day period. On this the urticaria subsided after the second day; however, fifteen hours after cessation of steroid medication the urticaria reappeared. Again an intensive search was made for possible allergens and emotional factors, but to no avail.

In the meantime, three more stool examinations were made, all revealing many *Giardia lamblia* cysts.

Fumagillin (Fumidil) was administered in the dose of 20 mg. four times daily for ten days. Daily stool examinations showed no *Giardia lamblia* after the third treatment day. The urticaria likewise subsided on the third day of treatment. No medication other than fumagillin was administered, and the results of the stool examinations were not divulged to the patient. One week after cessation of treatment urticaria recurred again,

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generalized as before. Stools again were loaded with *Giardia lamblia* cysts. At this point, stool specimens were obtained from the patient's two children and his wife; the stools of both children were negative but those of the patient and his wife were positive. A second course of fumagillin was given, 20 mg. four times daily for fourteen days, to both the patient and his wife, who was asymptomatic. Again, one week after the cessation of this second course of fumagillin therapy, severe urticaria recurred on the patient and his stools again revealed many cysts of *Giardia lamblia.*

At this time 100 mg. of quinacrine hydrochloride (Atabrine) three times daily was prescribed by another physician, together with tripelennamine hydrochloride (Pyribenzamine), 50 mg. four times daily. Stools on the first and second treatment days were positive, but remained negative after the third treatment day. On the third day the patient had severe diarrhea, but did not discontinue quinacrine medication. The urticaria subsided on the second treatment day and has been completely absent since. The quinacrine treatment was given for fourteen days; tripelennamine was discontinued after the fourth treatment day. The diarrhea due to quinacrine subsided after cessation of drug treatment.

Since then the patient has been followed for six months. Neither urticaria nor giardiasis has recurred.

CASE 2.—A 34-year-old white woman was hospitalized for right upper quadrant pain of three months' duration, associated with mild diarrhea. Past history revealed, aside from the usual childhood diseases, repeated bouts of "pneumonia." Nine years previously a "renal fixation operation" was performed for a "floating kidney and repeated urinary infections." There was no past or family history of allergy. The system review revealed bilateral occipital headaches, tiredness, nervousness, anorexia, and diarrhea, all of about three months' duration. During this time the patient lost 19 pounds (her weight dropped from 138 pounds to 119 pounds). There was a history of intolerance for highly seasoned foods, cabbage, and radishes. Three days after admission to the hospital, with no medication given, a "rash" occurred which was not noticed by the physician. Since her diarrhea and right upper quadrant pain were less distressing, she was discharged from the hospital, to be followed as an outpatient. Five weeks passed in which she had what, on questioning, appeared to have been constant urticaria, associated with severe generalized pruritus and a mild diarrhea. This became progressively worse and she sought consultation after the fifth week. Tripelennamine and diphenhydramine had been employed previously by other physicians, but no relief was noted.

On physical examination, the patient appeared in acute distress because of severe generalized pruritus, most marked on her palms. The nasal mucosa appeared pale with minimal serous rhinorrhea, the eyes appeared negative, minimal seborrhea of the scalp was noted, and a nephrotomy scar was seen on the right side. A cystocele was present. The liver had a sharp margin which was palpable one fingerbreadth below the right costal margin. There was some tenderness over the gallbladder area. The gallbladder was not palpable and the rest of the abdominal examination was negative. Generalized urticaria was noted, similar in type and distribution to that described in Case 1.

Laboratory examination revealed a normal white blood count on two occasions; the eosinophils numbered 3 per cent on the first differential slide and 7 per cent on the second. The sedimentation rate was 22. Liver function tests and x-ray examinations of the gallbladder, chest, abdomen, and upper gastrointestinal tract failed to contribute any information. Repeated urine analyses showed 2 plus albuminuria, presumably due to the chronic renal disease mentioned before. Stool examination was positive for *Giardia lamblia* cysts. Skin tests were noncontributory.

Course of Treatment.—The patient was given fumagillin, 20 mg. four times daily for ten days. Daily stool examinations became negative for *Giardia lamblia* on the third day of treatment but, although the severity of the pruritus and the extent of the urticaria diminished, there were still symptoms on the eighth day of treatment. Elimination of the few foods which had given skin reactions was carried out at this time. Since urticaria was

still present on the fifteenth hospital day, the patient was allowed a full unrestricted diet. Fumagillin was stopped and 100 mg. quinacrine hydrochloride (Atabrine) three times a day was started. In this case, stool examinations were already negative when quinacrine was started and remained negative, although urticaria continued to be a distressive feature. On the third day of treatment with quinacrine the urticaria disappeared and has not returned during a four-month observation period. No recurrence of positive stools was noted and the original complaint of upper right quadrant pain, diarrhea, weakness, and headaches was no longer present.

DISCUSSION

The correlation between urticaria and *Giardia lamblia* appears to me rather interesting and worthy of note. This group of parasites is usually not associated with peripheral blood eosinophilia. It is assumed that the organism of *Giardia lamblia* was responsible for the urticaria. The possibility exists, however, that fumagillin and quinacrine exert a direct effect on the urticaria. Nothing is known suggesting such an effect, but it is known that quinacrine is a strong inhibitor of cholinesterase.[5] I fail to see a relationship between this feature of the drug and the present problem under discussion.

Since asymptomatic carrier states are quite common in giardiasis, stool examinations usually are not performed in the absence of gastrointestinal symptoms. Even if they are performed and are reported as negative, as in Case 2, antigiardia medication, such as quinacrine (Atabrine), abolished urticarial symptoms. A review of the literature on giardiasis, including a review article of Piringer,[3] fails to reveal any suggestion that urticaria may be a possible manifestation of giardiasis. Other cases in which urticaria and giardiasis were found to be present were reported recently by letter.[4] Fat and vitamin A absorption appeared defective and excretions of bile were below normal in these patients infected with *Giardia lamblia*. This is attributed to mechanical effects of these parasites on the intestine. After my experience with giardiasis I cease to believe that this parasite is a normal nonpathogenic inhabitant of the human gastrointestinal tract.

SUMMARY

Two cases have been described in which urticarial episodes correlated well with the presence of *Giardia lamblia* in the stool. Treatment of the giardiasis was followed by disappearance of the urticaria. Upon return of the giardia in the stool, the urticaria also returned. The treatment of choice appeared to be quinacrine hydrochloride (Atabrine).

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CARDIAC ASTHMA

Some Practical Clinical Observations

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PAROXYSMAL dyspnea and cardiac asthma are not synonymous terms, although they are commonly used as such.[2, 4, 23] *Cardiac asthma* means paroxysmal left heart failure with asthma. *Paroxysmal dyspnea* can be used to designate paroxysmal left heart failure without asthma. In this clinic, *asthma* means wheezing with dyspnea.

Differentiation between these two manifestations of left ventricular failure has practical clinical importance. In the absence of asthma, treatment is limited to the disciplines of the cardiologist. In the presence of asthma, the disciplines of the allergist and the cardiologist may be needed for maximum relief.

In support of this thesis, which is not a new one,[5, 17] the records of twenty-six patients were selected for detailed analysis. All of them (1) had cardiac asthma, that is, acute paroxysmal left heart failure with asthma, (2) had improved after digitalization, and (3) had comprehensive allergy *and* cardiac evaluation.

The records were analyzed for evidence of allergy, infection, heart disease, and results of therapy. The data obtained from each case record are summarized in Table I. The incidence of each of the listed criteria is given in the first instead of the last column to facilitate evaluation of the table. Particular attention is called to the facts that eighteen had preceding asthma from other causes, twenty-five (all but Case 1) had other manifestations of an allergic background, fifteen had evidence of respiratory infection, all had some evidence of heart failure (usually from arteriosclerotic heart disease, with or without hypertension), only six were relieved adequately by cardiac therapy alone, and the others required cardiac *and* allergy management for maximum relief.

More detailed analysis of the data led to a number of simple, practical clinical observations, most of which have received little or no prior emphasis. Seven of the observations are from the point of view of the cardiologist and

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seven are from that of the allergist. They are illustrated by appropriate references to the table and by four case reports. The conventional ideas about cardiac asthma and the limited contributions of the allergist are summarized in the discussion.

A. PRACTICAL CLINICAL OBSERVATIONS: FROM THE POINT OF VIEW OF THE CARDIOLOGIST

1. *Treatment of heart failure may be all that is necessary,* since heart failure may be the only important precipitating factor in the asthma. This was true in six of the twenty-six cases (Table I, line 27).

2. Rapid unexplained *fluctuations in weight* in older asthmatic patients suggest cardiac asthma, especially when a gain accompanies exacerbations and remissions follow weight loss. Older asthmatic patients should be weighed regularly with this in mind. The report of Case 22 illustrates this point.

3. *Weight loss coincident with improvement,* following digitalization or diuresis, confirms the suspicion of cardiac asthma when clinical evidence of heart disease is equivocal. This was seen in Cases 17, 22, 23, and 26. Nineteen additional patients with definite congestive failure lost from 6 to 35 pounds immediately after digitalization and coincident with improvement (lines 20, 21, and 22).

4. *Moist basal râles and x-ray evidence of pulmonary congestion* during attacks of dyspnea with wheezing suggest cardiac asthma. Moist basal râles were heard in ten cases (line 13). Six of these had pulmonary congestion, according to x-ray evidence, while the congestion but not the râles was observed in three others (lines 13 and 14).

5. *A significant fall in blood pressure, concomitant with relief of an attack,* is strongly suggestive of cardiac asthma. This was observed in eleven of the fifteen hypertensive cases (lines 23 and 25).

6. *Cardiac asthma may occur before left ventricular failure is readily demonstrable.* The diagnosis is difficult then. The problem is illustrated in the report of Case 26.

7. *Cardiac asthma occurs chiefly in those conditions which lead to left ventricular failure.* Eleven of these cases had arteriosclerotic heart disease and fifteen had hypertensive and arteriosclerotic heart disease. Two of the arteriosclerotic group had what was interpreted as cor pulmonale with secondary left ventricular failure (lines 24, 25, and 26). Rheumatic and syphilitic heart disease were not encountered in these cases, although they were in an earlier series.[17]

B. PRACTICAL CLINICAL OBSERVATIONS FROM THE POINT OF VIEW OF THE ALLERGIST

1. *Cardiac asthma may be relieved temporarily by allergy management and conventional symptomatic asthma remedies.* This was striking in Cases 1, 22, and

TABLE I. SUMMARY OF ANALYSIS OF TWENTY-SIX CASES OF CARDIAC ASTHMA

CRITERIA	TOTALS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Allergy Data																											
1. Preceding asthma	18	0	+	+	0	+	+	0	+	+	+	+	+	0	+	0	+	+	0	+	0	+	+	0	+	+	0
2. Hay fever	12	0	+	+	+	0	+	0	0	0	+	0	0	0	+	0	+	+	+	0	0	+	+	+	+	0	0
3. Inhalant history, positive	19	0	+	+	0	+	+	0	+	+	+	0	+	+	0	+	+	+	+	+	0	+	+	0	+	+	0
4. Food history, positive	3	0	0	0	0	0	0	0	+	0	0	0	0	0	0	+	0	0	0	+	0	0	0	0	0	0	0
5. Allergic mucous membranes	11	0	0	0	0	+	+	+	+	+	0	0	0	0	0	+	+	0	+	0	0	+	+	0	0	0	0
6. Skin tests, positive	20	0	+	+	+	+	+	0	+	+	+	0	+	+	0	0	+	+	+	0	+	+	+	+	+	+	+
7. Family history, positive	9	0	0	0	0	+	+	0	0	0	0	0	0	0	0	0	+	0	0	+	+	0	+	0	0	+	+
8. Nasal polyps	8	0	0	0	+	+	+	+	0	+	0	0	0	0	0	0	0	0	+	0	0	+	0	0	0	0	0
9. Physical allergy history, positive	17	0	0	0	+	0	+	0	0	0	+	+	+	+	0	+	+	+	+	+	0	+	+	0	+	+	0
Infection Data																											
10. Infections (sinus or chest)	15	0	+	0	+	+	+	+	+	0	0	0	+	+	0	0	+	+	+	+	0	+	+	0	+	0	0
11. Infected nasal membranes	6	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	+	+	+	0	0	+
Cardiac Data																											
12. Gallop rhythm	3	+	0	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+
13. Basal râles	10	+	0	0	+	0	0	+	0	+	0	0	0	0	0	0	+	0	+	+	0	0	0	0	+	+	+
14. Pulmonary congestion (x-ray)	9	0	0	0	0	0	0	+	+	0	0	+	0	0	0	0	0	0	+	+	0	+	0	−	+	+	+
15. Cardiac enlargement	14	0	0	0	0	0	+	+	0	+	+	+	0	+	+	+	0	+	+	+	0	+	+	0	0	+	0
16. Peripheral edema	20	+	+	+	+	+	+	+	+	0	0	+	+	+	+	+	0	0	+	+	+	+	0	+	+	+	0
17. Hepatomegaly	11	+	+	0	+	0	+	0	+	0	0	0	0	0	0	0	+	0	+	+	0	+	0	0	+	+	0
18. Abnormal ECG	15	+	+	+	0	0	0	+	0	+	+	+	0	+	+	0	0	−	+	+	+	+	+	−	−	+	0
19. Hypertension	15	+	+	0	+	+	+	+	+	+	0	+	0	0	+	0	0	0	+	+	0	+	+	0	0	0	+
Response to Therapy																											
20. Weight loss	24	+	+	+	+	+	+	+	+	+	−	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+
21. Subjective improvement	26	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
22. Decrease or loss of wheezing	26	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
23. Decreased blood pressure	11	−	0	0	+	+	+	+	0	+	0	+	0	0	+	0	0	0	+	0	0	+	+	0	0	0	+

Types of Heart Disease																												
24. Arteriosclerotic	11	0	0	+	0	0	0	0	0	0	+	0	+	0	+	+	0	0	+	0	0	+	+	0				
25. Hypertensive and arteriosclerotic	15	+	+	0	+	+	+	+	+	+	0	+	0	0	+	0	0	+	0	+	+	0	0	+				
26. Cor pulmonale with left ventricular failure	2	0	0	+	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0				
Effective Therapy																												
27. Cardiac alone	6	+	0	0	0	0	0	0	0	0	0	+	0	+	0	0	0	+	0	0	0	0	0	+	0			
28. Allergy and cardiac	20	0	+	+	+	+	+	+	+	+	0	+	0	+	0	0	+	0	+	+	+	+	0	0	+			
a. Cardiac added to allergy	14	0	+	+	+	+	+	+	0	+	0	+	0	0	0	0	0	0	+	+	+	0	0	+				
b. Allergy added to cardiac	4	0	0	0	0	0	0	0	0	+	0	0	0	+	0	0	0	0	0	0	0	0	0	0				
c. Both initially	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	0	0	0	0	0	0	0				

Ages, 43 to 79 years.
Average age, 57.5 years.
0 = Negative or absent.
+ = Present or positive.
- = Not observed.

26 and less so in five others (Cases 2, 5, 6, 10, and 20). This observation was made in retrospect and the failure to appreciate this was an important deterrent to prompt recognition of the proper diagnosis in these cases.

2. *Asthma may be precipitated, in a cardiac patient, by infection and may be relieved by antibiotics.* The differentiation between infectious and cardiac asthma may be difficult. Both types of asthma should be suspected when older patients wheeze. The report of Case 22 illustrates this. Control of infection in the sinuses or bronchi seemed of major importance in the relief of asthma in fourteen additional cases in line 10.

3. *Asthma and heart disease may run their courses independently,* neither seeming to influence the other. This is not cardiac asthma, although it is commonly diagnosed as such. This is illustrated in Case 8 (not given in detail). After the initial episode of cardiac asthma was controlled, asthma recurred without heart failure and heart failure recurred without asthma. This has been observed previously,[17] but a satisfactory explanation has not been offered.

4. *Asthma from other causes may precede cardiac asthma* by many years.[17] This was observed in eighteen patients (line 1).

5. *Cardiac asthma is not always as severe and dramatic as in the classical description.* Cardiac asthma began as an unexplained increase in the intensity of existing asthma or as mild asthma which became severe in twenty of the cases (lines 13 to 18).

6. *Asthma which persists after control of left ventricular failure is usually due to noncardiac* causes which must be looked for systematically. Evidence of an allergic background was obvious in twenty of these cases and was suggestive in five others (lines 1 to 9).

7. *The maximum improvement obtained required combined cardiac and allergy management* in twenty of the cases (line 28).

CASE REPORTS

The following case reports illustrate most of the clinical observations.

Case 1.—This was a case of pure cardiac asthma, in which allergy was not important. There was no evidence of allergic background. There was a good response to digitalis alone. This case of classical cardiac asthma illustrates observations A, 1, 3, 4, and 7.

A 55-year-old man, in good health until nine months before admission, developed acute dyspnea while at his usual work. One month later he had another attack. His physician found hypertension and asthma. Repeated subsequent attacks of wheezing were relieved by the usual symptomatic remedies for asthma. The attacks continued to increase in number and severity. He was started on cortisone two weeks prior to admission. He promptly became worse. When admitted, his blood pressure was 150/120 mm. Hg, pulse was 120 per minute, venous pressure was 230 mm. H_2O, and circulation time was twenty-five seconds (arm to tongue). He had diffuse wheezing, moist basal râles, gallop rhythm, and classical signs of congestive heart failure. An electrocardiogram suggested an old anterior myocardial infarction. Neither the history, physical examination, nor skin tests suggested allergy or infection. The patient was digitalized immediately and started on the other routine measures for heart failure. He had one typical attack of paroxysmal

nocturnal dyspnea on the night of admission. He was greatly improved the next day. His blood pressure was 180/110 two days later. He lost 17 pounds in ten days and the wheezing and dyspnea disappeared completely. No other treatment was necessary.

Case 22.—This case illustrates the roles of allergy, infection, and heart failure. (See observations A, 2, 3, 5, and 7, and B, 1 and 2.)

A 44-year-old man had had perennial asthma and hay fever, troublesome cough, frequent respiratory infections, and sinusitis for many years. Symptoms had been worse for the past three winters. Several inhalant and physical influences were known to cause asthma. The family history was positive for allergy. The blood pressure was 160/110. There were signs of sinusitis, early emphysema, diffuse wheezing, slight left ventricular enlargement, extrasystoles, and slight pedal edema. Skin tests were positive for numerous foods and inhalants. Several examiners thought that he did not have cardiac asthma. Allergy management and treatment of the sinusitis led to some improvement. His blood pressure returned to normal and he lost 27 pounds in a few weeks. The significance of the weight loss was not appreciated at the time. He continued to improve, except for exacerbations of asthma whenever he contracted infections in his sinuses or chest. His weight remained stable. Three years later attacks of paroxysmal nocturnal dyspnea with wheezing began. There were no signs of congestive failure, but the diagnosis of cardiac asthma was again suspected. Digitalization was followed by marked improvement, disappearance of wheezing, and a 9 pound weight loss. He had no further difficulty until a year later, when wheezing recurred and he began to have bouts of precordial pain. He died suddenly a few months later.

Case 24.—In this case involving prior asthma, the roles of allergy, infection, and heart failure are illustrated. Combined treatment was necessary. This illustrates observations A, 3, and B, 2, 4, 5, and 7.

A 59-year-old man had wheezing and dyspnea, which progressed to extreme orthopnea associated with swelling of the feet, legs, and abdomen. There were typical signs of congestive failure and asthma. He improved promptly and markedly after digitalization, and lost 13 pounds in five days. A few moist basal râles and mild wheezing persisted. An allergy investigation disclosed that perennial hay fever and asthma had occurred intermittently for ten years. Asthma had been precipitated by house dust, hay, wheat, and ragweed pollen, cigarette smoke, and respiratory infections for years. The sputum became purulent with the infections. X-ray examination of the lungs showed pulmonary congestion. The ethmoids were hazy in the sinus films. The electrocardiogram was interpreted as "digitalis effect or ischemia." His skin reacted to numerous food and inhalant allergens. The residual wheezing disappeared on a routine allergy program. He remained essentially well for four years. Asthma and heart failure recurred then when he contracted a severe respiratory infection. Antibiotics relieved this episode. He had had no asthma when seen a few months later.

Case 26.—In this case, difficulties in diagnosis and clinical observations A, 1, 4, and 5, and B, 1 and 5 are illustrated.

A 58-year-old physician "caught cold" and coughed for about three weeks. Three months later he noticed a little dyspnea on the golf course and occasionally at night; this increased gradually. Three months later he wheezed a little for the first time. This increased each night for two weeks. He wheezed during the day a few times in this period. He was first seen then. Each attack had been relieved by one dose of 0.3 c.c. of epinephrine. He had several food idiosyncrasies, occasional urticaria and angioneurotic edema, occasional attacks of migraine, and a positive family history of allergy. He had been unusually healthy until the year before, when he had a transient mild cerebrovascular accident.

Physical examination showed inflamed nasal and pharyngeal membranes, pendulous abdomen, moist râles in the bases and mucous râles in the interscapular area, objective and subjective dyspnea, but no asthmatic squeaks; blood pressure was 170/105 mm. Hg; heart

sounds were normal and the heart was normal in size. X-ray examination of sinuses and chest showed no sinus disease, normal heart size and shape, and possible pulmonary congestion. His skin reacted to a few food and inhalant extracts. Cardiac asthma was suggested by one consulting allergist, but was rejected by two cardiologists and another allergist. Detailed studies elsewhere one week later led to the conclusion: "Attacks of nocturnal dyspnea are due to allergic factors. There is no evidence of heart failure."

His next visit was one year later. Occasional bouts of paroxysmal dyspnea had continued, with and without asthma, whenever he exceeded his recognized exercise tolerance. Physical examination showed pulse 105; blood pressure 150/105; accentuated aortic second sound; transient gallop rhythm; and a few basal râles, but no squeaks. Digitalization was advised if asthma returned.

He was admitted one month later in an attack of paroxysmal orthpnea with typical asthma. His blood pressure was 190/132. He was digitalized. He lost 4 pounds promptly. His blood pressure, after digitalization, was 156/112. He had no more asthma or paroxysmal dyspnea thereafter. He died suddenly at home about one year later.

DISCUSSION

There are nine types of causes of asthma,[18] representing hundreds of individual etiological factors. Multiple types of causes are found in most cases of chronic asthma in this clinic. The importance of causes other than allergy and infection is thought to increase with age.[20] Cardiac asthma, due to acute left heart failure, is one of these.

Cardiac asthma is generally thought of as the dramatic syndrome described so vividly by McGinn and White[19]: "Cardiac asthma is a name applied to a kind of dyspnea peculiar to organic cardiac disease. For this particular condition it is distinctive, and it is preferable to such other terms as pulmonary edema or paroxysmal dyspnea, for it is truly asthmatic in nature and it is fundamentally of cardiac origin. Cardiac asthma is paroxysmal, coming on usually in sleep, but at times following exertion. An attack quickly rises to a peak, is accompanied by both inspiratory and expiratory difficulty, and frequently by a terrifying sense of suffocation which causes the patient to sit up or to stand erect, or even to go to a window for air. The attacks last from a few minutes to a few hours, averaging about an hour, and leave the patient in an exhausted condition for hours or days."

Osler,[1] Pratt,[2] Palmer and White,[3] White and McGinn,[13] Plotz,[7] Harrison and his associates,[4] Wolferth,[8] Weiss and Robb,[12] Vugrinčič,[23] and others have called attention to the following features of classical cardiac asthma: onset during sleep, fear of death, compelling desire for air, sweating, accentuation of the pulmonic second sound, elevation of blood pressure, fetal or gallop rhythm, tachycardia, signs of asthma, increased hilar shadows, reduction in vital capacity, increased volume of blood in the lungs, and prolonged lung-to-tongue circulation time. Osgood[15] called attention to the relative stability of the blood pressure in noncardiac asthma. Ferris[21] and Gelfand[22] have emphasized the difficulty in differentiating clinically between allergic and cardiac asthma.

Factors which tend to precipitate attacks and those which tend to shorten attacks of paroxysmal dyspnea have been presented by Harrison and associates,[4] Wolferth,[8] Brunn,[10] Perera and Berliner,[11] Vugrinčič,[23] Danzer,[16] Weiss and Robb,[12] and Swineford and Magruder.[17]

Factors which tend to precipitate attacks are: the supine position, decrease in serum protein concentration, resorption of edema fluid, an increase in venous pressure, a decrease in vital capacity during the early morning hours, cough, nightmares, abdominal distention, constipation, a full bladder, hunger, excessive warmth, lowering of the head during sleep, arrhythmias, overeating, outside noises, and, obviously, allergen exposures and infection. Harrison feels that the common factor is the conversion from the depression of sleep to the reflex hyperexcitability of awakening. This results in respiratory stimulation, increased ventilation, pulmonary congestion, reduced vital capacity, and a temporary imbalance between the right and left ventricular functions. If the factors which tend to precipitate or prolong an attack are not relieved, pulmonary edema may follow.

Factors which tend to alleviate attacks are: elevation of the head, alleviation of anxiety, proper weight and amount of bedclothes, measures to reduce abdominal or bladder distention, control of cough and infection, cardiac management, and a reduction in the allergic load.

As pointed out in the clinical observations, cardiac asthma is not always so vividly classical. Consequently, variations from the classical form may be difficult to diagnose, particularly in the absence of cardiac enlargement or anginal symptoms. Cardiac asthma should be suspected in any asthmatic patient who sweats profusely, goes to the window for air, has an abnormal left auricular or ventricular load, or is over 40 years of age. The diagnosis can be confirmed by evidence obtained during an attack or during a series of attacks. The diagnosis may be suspected, but cannot be made with certainty during periods of freedom from attacks.

During an attack the diagnosis is confirmed if there is (1) a prolonged lung-to-tongue circulation time; (2) unequivocal transient pulmonary congestion; (3) prompt relief from (a) venesection, (b) tourniquets on all four extremities, (c) positive pressure oxygen breathing, (d) nitroglycerin under the tongue when the attack is due to coronary insufficiency; or (4) if pulmonary edema, a step beyond cardiac asthma, develops. These observations are not made very often. As a result most cases are diagnosed by their response to cardiac management, that is, when a series of attacks is terminated by digitalization or diuresis. Decholin as a measure of circulation time is not without risk.

Cardiac asthma is usually due to left ventricular failure. Hence, distended neck veins, large liver, peripheral edema, and elevated venous pressure may be absent during an attack. Failure of the right ventricle, which leads to these signs, may relieve cardiac asthma temporarily. After the right heart fails, however, subsequent paroxysmal left heart failure may continue to precipitate attacks of asthma. It is generally accepted[2, 3, 4, 7-9, 12] that cardiac

asthma is precipitated by the pulmonary congestion which accompanies acute left ventricular failure. It is surprising that mitral stenosis, which leads so often to acute pulmonary congestion, is so seldom associated with cardiac asthma. This has been discussed by White and McGinn,[13] Lombardo and Harrison,[9] Vugrinčič,[23] Gelfand,[22] and others.

The literature, as shown above, provides an excellent picture of cardiac asthma from the point of view of the cardiologist. Contributions by allergists have been feeble by comparison. Little has been added since Harkavy[5] showed the need for cardiac and allergy management, Rackemann[6] emphasized the frequency with which cardiac patients do not wheeze, and Swineford and Magruder[17] called attention to some of the differences between cardiac asthmatics and emphasized the role of allergy. It is to be hoped that this problem will receive the added attention it deserves in the near future.

The differences between patients with concurrent asthma and heart disease were noted in a previous study.[17] They were classified into two main groups—those with troublesome and those with mild asthma. Each of these groups was subdivided into those who had had asthma for a long time before heart disease developed and those in whom the priority of asthma was questionable. They were further subdivided into those with and without congestive failure and those aggravated by or unaffected by the advent of cardiac symptoms. They were further classified on the basis of the type of heart disease. Some such classification as this has practical value. For example, a long history of asthma would suggest a major role of allergy or other noncardiac causes. On the other hand, asthma which did not precede other cardiac symptoms would suggest a major role of heart failure.

Swineford and Magruder[17] felt that wheezing with paroxysmal nocturnal dyspnea is an indication, in the majority of cases, that the patient has previously had asthma or that he is an allergic person in whom the onset of asthma is provoked by the loss of cardiac reserve. This is confirmed by lines 1 to 9 in Table I. This idea is germane to the management of cardiac asthma, as it implies the need for comprehensive evaluation of the asthma as well as the heart disease.

The only therapeutic agents which have diagnostic value in cardiac asthma are digitalis analogues, diuretics and, perhaps, nitroglycerin. They may relieve cardiac asthma but never help any other kind of asthma. The use of and the response to epinephrine and aminophylline or their analogues, aerosols, Demerol, or opiates are of no diagnostic value.

Reluctance to use epinephrine for cardiac asthma is widespread. Small doses, 0.2 c.c., are used freely and effectively in this clinic. The usual response is prompt relief of the attack with slowing of the pulse and lowering of elevated blood pressure. No untoward reactions have been observed, nor have adverse reports been found. Levine[24] used 0.5 to 1.0 c.c. of 1:1,000 epinephrine to elicit angina pectoris in susceptible subjects. This is 2.5 to 5 times the proper dose for any type of asthma. Schofield and Walker[26] showed that small amounts of epinephrine increased coronary blood flow.

While opiates are universally recommended in cardiac asthma, numerous deaths in asthmatic patients have been attributed to their use.[25] In this clinic opiates are used only after the diagnosis of cardiac asthma has been confirmed. Epinephrine, 0.2 c.c., is used in allergic and infectious asthma and in all cases in which the etiology is not known. Aminophylline is given intravenously when epinephrine has failed to bring relief. At least two patients with cardiac asthma have died in this institution while receiving aminophylline intravenously.

SUMMARY AND CONCLUSIONS

Twenty-six cases of cardiac asthma were analyzed for evidence of allergy, infection, heart disease, and results of therapy. The data from each case are summarized in a table. The following points are emphasized:

The term *cardiac asthma* should be limited to paroxysmal left ventricular failure with wheezing. Paroxysmal orthopnea without wheezing is not cardiac asthma.

Cardiac asthma is not a simple syndrome. There are, usually, other important considerations in addition to the heart failure. Control of the manifestations of allergy is usually a necessary supplement to cardiac therapy. Only six patients were relieved adequately by cardiac therapy alone. The others required additional treatment of allergy and/or infection.

Analysis of the data led to fourteen simple, practical, clinical observations. Seven are from the point of view of the cardiologist; the others are from that of the allergist. These are illustrated by references to the data in the table and by four case reports.

Acute left heart failure is one of nine types of causes of asthma and is usually associated with one or more of the other types of causes.

Current ideas about cardiac asthma are summarized in the discussion. These are based on contributions by cardiologists primarily. Allergists have not emphasized the noncardiac aspects of the problem sufficiently. Cardiac asthma needs much more study.

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American Academy of Allergy

THE CHANGING PICTURE OF ALLERGY

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I BRING you greetings from the Officers and Fellows of the American College of Allergists. Some years ago, the Academy and the College inaugurated an era of mutual friendship and good will by an annual exchange of presidents. By doing so they gave honor always to the position, usually to the incumbent, and frequently to both. I hope that this pleasant custom may continue for as long as there are presidents to exchange. Although it may appear sometimes that the aims of the two societies are diverse, actually we are single minded in our purpose to advance the cause of allergy.

Those who hold office in our two national organizations have two adjustments to make. The first is to become accustomed to being conspicuously miserable. I am reminded, in this regard, of a man who had been tarred and feathered and run out of town on a rail. When he was asked how he felt, the answer was, "If it hadn't been for the honor of the occasion, I could just as well have done without it."

The second adjustment is that of growing accustomed to the fact that for a period of twelve months many of our ordinary remarks appear to acquire special validity and significance. A discussion of the present becomes either "a pointing with pride" or "a viewing with alarm." A discussion of the past must be intimately historical or whimsically reminiscent. As for the future, the holding of office supposedly confers the power of prophecy. But enough of the personal and more of the purpose.

We want to consider the changing picture of allergy. For those who may have other business elsewhere, let me say that there will be two conclusions. One conclusion will consider allergy as having changed little. It can be said of allergy, as in French it can be said of sex and women's clothes, "The more it changes, the more it is the same thing." The second conclusion is that we perhaps know a little more and understand a little less. None of the fundamental problems have been solved. Ours is a dynamic specialty. We deal with the specific harmfulness of harmless substances. In this age of chemicals and synthetics there is truly no limit as to what substances may be discovered as causes of allergy. The lack of capacity of the tissues to react in new and different ways limits the number of types of reactions. Some of these, by definition

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only, are termed allergic. One antibiotic agent and one antihistaminic agent have, between them, been listed as causing almost every presently known type of allergic and non-allergic response. In taking this passing look at one aspect of allergy, namely, drug allergy, the reactions seen resulted from substances which had been rigorously tested. How truly reactive and allergenic must those compounds have been which did not get beyond the appraising committees and the first investigators!

It would appear, from an analysis of the present literature, that, except for new drugs and new synthetics, the major causes of allergy had probably all been discovered. This I do not believe. I can remember when molds were first considered as possible allergens, although they were suspected as such more than fifty years ago. The discovery of house dust as an allergen dates back less than forty years. It is not too much to expect that one or several new ubiquitous allergens may be discovered at any time. This would, of course, change overnight the present practice of allergy. Among these might be the more than 1,000 "additives" now ingested with foods and now certified for safety with regard to toxicity but not to allergenicity.

One other such possibility would be the satisfactory proof of the allergenicity of so-called nonpathogenic bacteria. Yet another possibility would be the proof that the currently unculturable molds cause allergenic responses. Another would be the proof that degradation products of everyday substances cause allergy, although tests and exposure to the whole natural substance do not. There is some evidence that this may be true. On the basis of work in progress, the opposite may also be true—that is, that there are no truly allergenic substances, but merely patients who are more or less allergic.

We must remember that the *Penicilliums* and their antibacterial effects were first noted by Tyndall in 1881 and that the term *antibiosis* was first suggested by Paul Vuillemin in 1889. In the sixty years between 1881 and 1928, when Alexander Fleming's trained but curious eyes realized what they were seeing, no one else saw the potentialities for good. These could just as easily have been potentialities for harm.

At present, our progress in certain aspects of our specialty appears to be speedy. It is truly so with regard to drugs for treatment purposes. Actually, it has been slow, and we can tell how slow only by pausing to look backward. Just as the antibiotic agents have caused a measurable deterioration in the general level of the practice of medicine, the antihistaminic agents and the steroids have caused similar depreciation in the practice of allergy.

Allowing for this, is there any way in which we can see how far we have traveled? For this purpose, let us choose a reasonable period of approximately twenty-five years. This span represents the time that I have been exposed to allergy. The year 1931 saw the publication of the great classic American text, *Asthma and Hay Fever in Theory and Practice* by Coca, Walzer, and Thommen (Charles C Thomas, Springfield, Illinois, publisher). Here is a good milepost.

You will find, I think, a discussion of the practice of allergy of a quarter of a century ago interesting and yet perhaps a little disturbing. To appreciate

it to the full, however, we must go back a little further into the history of our specialty, as this is the only way in which we can understand the background of this great book.

Let me remind you that anaphylaxis was first described by Richet 69 years ago. Within five years (that is, by 1903), Arthus had described the phenomenon named for him. And, by 1905, Theobold Smith had proved that guinea pigs could be sensitized to horse serum. By 1907, fifty years ago, Nicolle and all, separately, Friedman, Richet, and Otto had proved the existence of antibodies. By 1908, passive transfer in animals had been described and measured.

Between 1910 and 1912, the Schultz-Dale technique had been perfected and the *qualitative* studies proving the presence of these various allergic states were followed by *quantitative* determinations. It was known then, forty-five years ago, and is not as yet fully appreciated today, that $\frac{1}{20,000,000}$ gram of egg albumin and $\frac{1}{1,000,000}$ mm. of horse serum were sufficient for sensitizing purposes.

In 1921, thirty-five years ago, Prausnitz and Küstner published the results of their famous experiment. In 1926, thirty years ago, the immune body had been discovered and it was then known that the blood of immunized animals protected sensitized animals against specific antigens. In 1926 Lewis, and in 1927 Dale and Best, studied the reactions mentioned and showed them, in many respects, to be qualitatively and quantitatively similar to those induced by exposure to histamine. They did not prove that the reaction was due to histamine, but it must be admitted that they made their hypothesis appear pretty plausible.

It is obvious, therefore, that between sixty and twenty-five years ago not only the basic immunology, but every major immunologic discovery in our field, had been made. And it was twenty-five years ago that Coca asked a deceptively artless question: "Why do so few patients become sensitive to the so-called 'good antigens' as for example, egg and animal danders to which they have frequent exposure, as compared with the many who become sensitive to 'poor antigens' as pollens and contactants?" The answer to this question will be one of the major discoveries of the future.

We cannot cover all of the field of allergy. Let us, therefore, limit ourselves to one specific disorder so that we can again measure our rate of progress. What have we learned, for example, of the etiology of bronchial asthma?

In 1755, twenty years before our Revolutionary War, Haller knew that lung tissue responded to irritation with contraction. Vermier, in 1779, proved that exposure to irritant gases could cause bronchospasm. Bronchial collapse, as known to be due to muscle contraction, dates back to Reiseisen in 1822 and its fairly exact measurement to Donders in 1853, that is, over a century ago. When it was discovered that bronchospasm could be caused by stimulation of the vagus, it was concluded that bronchial asthma was a neurological disorder and, by inference, a neurotic one, although today we differentiate between neuronic and neurotic responses.

Back in 1819, Laennec wrote that asthma was precipitated by bronchitis, by emphysema, and by "dry catarrh." These three caused irritation of the nervous system. The nervous system reacted with spasm of the bronchioles.

However, in 1886, Clark suggested that asthma was an angioedema of the mucous membrane of the lung. This was actually seen bronchoscopically and vividly described twenty years later, that is, in 1905, by Pieniozek.

There were many other theories based on supposed pathologic findings. None have stood the test of time. In 1931, however, the two theories (that is, spasm versus edema) were being referred to by Coca, Walzer, and Thommen as "a time-worn debate." That both states occur there is no doubt. But whether they occur simultaneously or in succession, and which comes first, remains today a matter of question.

Up to 1931 there were, in the world literature, evidently only thirty-three recorded autopsied deaths from bronchial asthma. No conclusions could be drawn from the pathology of these. There were evidently deaths of many types of asthmatic patients and there were no obvious differences between them.

Since they could not depend upon pathologic data, Coca, Walzer, and Thommen were thorough in seeking etiological causes. They discussed frequency, mortality, morbidity, race, sex, age distribution, climate, soil, altitude, geographical distribution, season and temperature changes and also social conditions and occupation as playing a part in the etiology of bronchial asthma. None of these causes had been satisfactorily measured then. All, as issues, remain unsettled today.

Coca, Walzer, and Thommen discussed, as well, heredity, endocrine factors, clinical and physical factors, metabolic and nervous and psychic factors, and the famous "exudative diathesis theory" of Czerny which dates back to 1905. All that the exudative diathesis theory says is, "If you are the type of patient afflicted with this type of disorder then this is the type of disorder which will afflict you."

Also, the nonimmunologic or extremely opposite point of view (that is, that psychic factors actually cause asthma) was discussed as much twenty-five years ago as it is today.

In present-day journals (the editors of which should know better) there are papers (by physicians who should also know better) stating that not only asthma, but all allergy as such, is "psychosomatic." There is, no doubt, a great deal of psychopathic, psychoneurotic, and psychosomatic illness. Strangely, or perhaps not so strangely at that, it always seems to play a large part in the other physician's specialty. The less one knows of any aspect of medicine, the more likely one is to believe that it is all psychosomatic. A neurotic patient is evidently one in whom one achieves a poor result or else one who is more neurotic than his physician. Much of this literature is excellent fiction. Of this type of writing, what is good is not original and what is new is not good.

A long time ago, in 1882, Kirshbaum again made the same suggestions. And every year thereafter until 1927 there were published a number of papers

dealing with this subject. Impetus was given to the so-called neurosis theory by Hansen, who used hypnosis to treat asthma in 1927, and by Zingler and Elliott, who in 1928 first used a pneumograph to measure changes in lung volume as due to emotion.

There is no doubt that there are changes in lung volume due to emotion and also that there are changes in lung volume due to asthma. But because both may be similar, how simple, how easy, and how obvious it is to jump to the superficial conclusion that both are identical and that the emotion must, therefore, cause the asthma. As a matter of fact, our own work has shown that emotion can both increase and decrease vital capacity and both lessen and cause bronchial spasm.

To stand on neutral ground, let us use angina pectoris as an example. There are a narrowing of the coronary arteries and spasm due to hypoxia of the cardiac muscle. In an attack of anger, there is a demand for cardiac oxygenation which the narrowed spastic vessels cannot satisfy. The pain, the physical findings, and the electrocardiogram are all those of angina pectoris. Who would conclude, therefore, that angina pectoris is purely psychosomatic and due to emotion because emotion induces attacks indistinguishable from those which otherwise occur? As I have said elsewhere, emotion does not *cause* physiologic changes. It is, in itself, a physiologic change. How often in allergy do we conclude, and erroneously, that because two things are similar they are identical? We must not jump to the conclusion that, because two similar results follow two separate causes, the causes are, therefore, identical. That this type of reasoning is fallacious is obvious to any thoughtful observer.

It is said that if one alters the personality, changes the internal environment by the administration of tranquilizing agents, or changes the external environment by eliminating the conflict, then one can eliminate the degenerative process. Unfortunately, biologic reactions are, as a whole, degenerative and go only in one direction in time and not one of the experiments can be controlled because the questions asked are nonoperational.

You will remember Freud's famous patient who wept on the day she was being discharged following a successful analysis of ten years' duration. Her famous question must echo in the minds of many of us. "What good is it to be the only adjusted person in a completely maladjusted world?" That is enough to make anybody neurotic! The treatment of choice is, of course, another ten years of psychotherapy.

The best rebuttal to these arguments is to take, not the example of bronchial asthma since spasm may be due to many diverse causes including the emotional, but rather a completely proved allergic disorder like hay fever. Is it possible that millions of ragweed-pollen-sensitive patients, no matter where they are, show signs of reaction only when pollen is present? Are they demonstrating a mass neurosis because summer vacations are over and they do not wish to face the harsh realities of work or winter? The theory has been seriously advanced that the neurosis comes first and that the pollen is a trigger mechanism. But

why just the one pollen and not another pollen? And why the spring, or the summer, or the fall, or any one or two, or all three? This aspect of the nasal neurosis theory is rarely the subject of discussion.

In 1928 John Freeman said that removing the sensitivity or eliminating the allergen cleared the disorder.

In 1931, Coca, Walzer, and Thommen said, "It is doubtful whether further investigation in the field of psychology will ever clear up the mystery of the basic mechanism of bronchial asthma."

Let us have it that all patients are psychoneurotic and that the best treatment is both antiallergic and antineurotic.

What has the passage of time taught us about skin tests?

Inhalation tests for hay fever date back to Kirkman, who, in December, 1835, while in a greenhouse, inhaled the pollen of sweet vernal grass and induced an attack of hay fever. In 1865, Blackley performed conjunctival tests, scratch tests, and insufflation tests.

Then came the era of the "nasal neurosis theory" which held the field against all others for thirty years. During this time there was little progress in the field of allergy.

In 1903 Dunbar proved the specificity of the conjunctival test. In 1909 Smith reported on a patient with buckwheat sensitivity proved by positive scratch tests which caused both a large, local reaction and, as well, a constitutional reaction with asthma, urticaria, and angioedema. The control tests with wheat were negative.

In 1912 Schloss put the intradermal test into the position of a standard procedure when he used it both qualitatively and quantitatively to study an egg-sensitive patient. By 1913 Clowes had done intradermal tests with ragweed pollen extract and by 1915 and 1916, forty years ago, the skin test technique had been perfected by Cooke, his associates, and colleagues.

In discussing asthma from the skin test or immunologic point of view, our three authors say something that no allergist should ever forget. They include both "sensitive and nonsensitive" patients in the same group as having true asthma because they say, "Both types are frequently found among members of the same generation and in one family and also nonsensitive asthmatics may be the progeny of sensitive asthmatics and vice versa."

"It is not at all uncommon," they say, "to find among some middle-aged, nonsensitive 'infectious' asthmatics an undeniable past history of typical hypersensitiveness."

"It is unreasonable," they continue, "to exclude such a patient from the ranks of the true bronchial asthma merely on the grounds that he manifests no positive cutaneous reactions at this time." In my practice I have consistently found them to be right.

It is amusing to recall that skin tests, as used for discovering sensitivity, were not generally accepted thirty years ago. At Wiesbaden, in 1926, at the

International Symposium on Asthma, the greatest internists then in practice unanimously criticized and condemned the diagnosis of bronchial asthma by skin tests and published a report putting their opinion on record.

They were wrong then, as they are so often wrong now. It has been said that if we were good internists first and allergists second, there would be no allergy. History proves the errors in knowledge and judgment to be more often the internists' than the allergists.' Although the two specialties are far from being mutually exclusive, at present it appears that we have much more to teach the internists than they have to teach us. For just so long as more patients go from internists to allergists than the other way around, our specialty is safe.

Although time has given us better extracts, we must conclude that the skin test techniques established and perfected between fifty and twenty-five years ago have not been improved upon.

Perhaps if our techniques have not changed, our treatment by injection has. Coca, Walzer, and Thommen have this to say:

"As the procedure merely induces a raised threshold of tolerance, its success will depend on the degree of the patient's clinical sensitivity, the amount and the nature of the atopen to which he is exposed and his response to treatment. Although of unquestionable benefit, hyposensitization treatment still fails to approximate the ideal results which might be attained by true desensitization. It usually does not furnish results as satisfactory as those attained by complete avoidance of contact with the offending substance."

To this 25-year-old evaluation of the results of our treatment techniques by injection we can add very little.

Has our attitude toward the role of infection changed any in the same twenty-five years?

In 1931 there were, as you know, no true antibiotic agents available. Coca, Walzer, and Thommen warn us against halfway measures. They say, "The removal of adherent mucus and secretions and the cleansing of the mucous membrane are as important as any other factors in the production of the favorable results frequently obtained." Can anyone suggest any better treatment available today?

Was their attitude toward vaccine therapy very different from ours?

The first paper dealing with vaccine therapy dates back to Farrington in 1911. Goodale, in 1916, advocated their use. In 1917 Gottlieb and in 1918 I. C. Walker tested patients with dry, bacterial proteins and reported immediate and delayed reactions. In 1922 Cooke and in 1923 Rackemann could not duplicate results.

In 1929 Sanford B. Hooker and Addison said, "The organisms may almost certainly be excluded as primary pathogenic invaders; their role as secondary agents of infection is probably very subordinate."

In 1931 Coca, Walzer, and Thommen said, "The specific diagnostic value of the bacterial protein skin tests in connection with atopic hypersensitiveness remains to be demonstrated." And so it does.

What drugs did physicians use before the age of the antihistaminic agents and the steroid hormones?

In 1819 pollinosis was treated with iron, mercury, quinine, opium, and digitalis.

As regards climatic changes, the United States Hay Fever Association, in 1874, adopted a constitution of which Article V reads: "It shall be the duty of each member to report to the Recording Secretary the discovery of any remedy, source of relief or exempt district which may come to his or her knowledge during their natural lifetime or afterwards, if permitted."

In 1876 asthmatic patients were treated with strychnine, belladonna, atropine, potassium bromide and iodine, caffein, ipecac, arsenic, thyroid, and suprarenal extract, which in one way or another has been in use for seventy-five years.

In 1880 Blackley first suggested arsenic and iodine. Little did he know what he was doing for the gaiety of the physicians of the largest city of Harrison County, Mississippi.

In 1886 pollinosis was treated by lowering the room temperature by hanging ice from the ceiling and by the prohibition both of alcohol ingestion and of the wearing of elastic garters. The exercise of "self-control" was strongly recommended by the embryo psychiatrists of that age.

In 1893 Ferber kept the ears contused, thereby reflexly stimulating the sympathetic nervous system. In 1894 Page suggested the wearing of as few clothes as possible.

But, in 1927, Pasteur Vallery-Radot reported on the treatment of asthma with intradermal injections of peptone. Flandin reported that autoserotherapy had been successful for fourteen years. Pokorny used x-rays to the root of the nose. Bonjour reported on morphine as effective in a study which had extended over a period of thirty-five years.

Coca, Walzer, and Thommen, however, discuss the use of cocaine, epinephrine, and ephedrine. Both ephedrine (reported on by Piness in 1927) and epinephrine have certainly stood the test of time. Cocaine is used only rarely, and then more often in the eyes and occasionally in the nose.

As a reminder and an echo of the difficulties met in introducing a new drug and of assessing its side effects, how modern does the following verbatim statement sound?

"Twenty-two percent of the cases observed were unable to take the drug because of the production of disagreeable symptoms. The most common untoward effects are palpitation, nervousness, visible tremor and internal agitation. Other effects are nausea, vomiting, insomnia, weakness, headache, urinary bladder irritability, throbbing in the occipital region and pharyngeal irritation. Althausen and Schumacher report the obtaining of undesirable effects in thirty

percent of their cases and in twelve percent the symptoms were so severe that the drug could not be given at all. Marked toxic effects were observed by Balyeat in twenty percent of his cases and Gaarde and Maytum found sixteen percent of their patients unable to take the drug."

To what drug is reference here being made? To a new antihistaminic agent? No! To a new chemotherapeutic agent? No! It refers to our everyday ephedrine. No reports on *its* side effects or toxicity have appeared for many years.

The allergists of twenty-five years ago did not always succeed in the treatment of their patients. What reasons did they give for their poor results?

Vaughan, in 1928, listed five causes of failure:

1. Superficiality—failure to take advantage of all the information available.
2. Ignorance on the part of the physician as to the fundamentals of theory and practice of the subject.
3. Poor judgment.
4. Insurmountable obstacles, such as emphysema, bronchiectasis, and sinusitis.
5. Lack of cooperation between patient and physician.

His paper could be published today. No one would guess that it was written long before many of us knew one end of a syringe from the other.

In their classic text, Coca, Walzer, and Thommen showed themselves to be well grounded in the history of their subject and to be perspicacious clinicians in their observance of what was true of their day. They were so accurate in these observations that what was true for them is equally true for us.

They also looked to the future. How accurately prophetic they were!

I would like to quote the last four lines of that section of their book which deals with the treatment of bronchial asthma:

"The public and the medical profession need to be aroused to the fact that a considerable amount of asthma is preventable. The time is not far distant when campaigns will be waged instructing the layman in the danger signals in asthma just as they are today in tuberculosis and other illnesses."

Twenty-five years later the American Foundation of Allergic Disease published its booklet on asthma.

In twenty-five years we have made some advances. Many of these have been in the direction of making our patients more comfortable more quickly, more easily, and more effectively. But research of the future must go back to the same old fundamental questions:

Why do mammals become allergic?

Why do they become allergic when they do?

Why do they become allergic to one substance and not to another?

The answers to these questions must be the concern of the thoughtful research-minded allergists of today and of tomorrow!

75 Bay State Rd.

Editorial

MORE ON CARDIAC ASTHMA

IN THIS issue the reader can indulge his interest in the highly important clinical entity, cardiac asthma, presented and discussed by Dr. Swineford and his group on page 354. Here two common clinical states, cardiac failure and diffuse obstructive disease with wheezing, combine to present the physician with a tangle of interacting cardiovascular and respiratory phenomena. On the pulmonary side of the problem, Dr. Swineford and his associates concern themselves solely with wheezing (used synonymously with asthma) associated with dyspnea. As defined by them, therefore, cardiac asthma has wheezing as an essential component and this is in accord with general usage.

Presentation of a somewhat different point of view at this time hardly requires justification when the subject under discussion is of special interest to allergists and, furthermore, is one concerning which there has always been a great deal of disagreement. The view adopted here is that cardiac asthma is only a special instance of diffuse obstructive disease of the airway associated with cardiac failure. Wheezing may be present in any condition in which diffuse obstruction of the airway occurs, although it is especially prominent in bronchial asthma. On the other hand, wheezing may also be minimal or entirely absent, even in the presence of marked diffuse obstruction of the airway, a very common occurrence in "idiopathic obstructive emphysema." Wheezing, therefore, is not a reliable indication of the degree of obstruction; nor is it particularly useful as a means of recognizing the nature of the obstructive process.

It is not difficult to see how asthma and other forms of diffuse obstructive disease, with the attendant increased respiratory work, might lead to cardiac failure. It is likewise not difficult to imagine that the pulmonary congestion associated with left-sided heart failure might act as a "nonspecific" irritant or stimulus which could induce the asthmatic response, whatever its precise nature, in an airway which has hyperreactivity as an outstanding characteristic. If one allows, in addition, the possibility that this hyperreactivity may wax and wane over a period of time, then one has conjured up the requirements for the independent occurrence of cardiac failure on the one hand and asthma on the other, in one and the same person, an instance of which is cited in the article, by Dr. Swineford and his co-workers.

The combination of cardiac and obstructive pulmonary disease would be expected to occur with increasing frequency in a population in which the number of persons in the older age groups is increasing. If, as seems highly probable, cigarette smoking is an important etiological factor in the pathogenesis of

"idiopathic obstructive pulmonary emphysema," a still further increase in this and in the combination of cardiac and obstructive pulmonary disease is to be anticipated. Since some of these patients have wheezing associated with cardiac failure, they may contribute in increasing numbers to the group given the label "cardiac asthma." Among this group will be persons who, in addition, have right-sided heart failure secondary to the pulmonary disease.

Some who feel themselves to be adept in the purely clinical, and who are entirely at home at the bedside, rely on the five senses along with the judicious use of the scales, a point well made in the article by Dr. Swineford and his group. Others will wish to go further and make measurements of pulmonary function. Is resort to the techniques and contraptions required justified, or will it merely serve to alleviate anxiety in the physician by supplying "facts and figures"? What can such measures tell the clinician that he cannot readily divine from bedside observation with a high degree of accuracy? And of what value is this information?

The answer to such questions pertaining to the heart is too well known to require comment. But what of the lung? How well is it doing the job of acquiring oxygen and eliminating carbon dioxide, and how much muscular work is being expended in the process? What is the nature of the pulmonary abnormality, and how can this be recognized and treated? There is ample evidence that these questions cannot be answered at the bedside. The reason for this is that a significant increase or decrease in minute volume may go unrecognized; resistance to airflow of extreme degree may occur without wheezing (ventilation imposing a heavy work load the while); abnormalities in distribution and diffusion are likewise unrecognizable; hypoxia will be recognized only when advanced; and the presence of carbon dioxide retention cannot be detected. X-ray examination of the chest will usually contribute little or nothing in the way of an answer to these questions.

The imposing nature of many tests applicable to the assessment of pulmonary function may constitute a strong deterrent to the performance of any test of pulmonary function in the sick patient. Complicated or prolonged tests are by no means always necessary, however. Fortunately, measurement of the blood carbon dioxide and the arterial oxygen saturation (the latter is often not essential) and a simple kymographic tracing of a maximal expiratory effort will supply much of the information required for clinical purposes. This last test can readily be carried out by all but the sickest patients and will give a quantitative measure of restrictive and obstructive disease, being especially valuable for assessment of the latter. The knowledge obtained by these procedures will not only contribute to a clearer understanding of the pulmonary component in cardiac disease, with or without wheezing, but it may point to both caution in the use of oxygen and sedatives and an urgent need for intensive treatment of the pulmonary abnormality, treatment which is often logically directed at alleviation of the obstructive defect with such measures as aminophylline and sympathomimetic drugs, with or without the administration of prednisone or prednisolone. Again, the therapeutic response to such a regimen

will be most clearly and accurately assessed by one or more subsequent recourses to laboratory measurements. The response to such therapy, as indicated by a change in these measurements, affords valuable additional information concerning the nature of the pathologic processes involved and is therefore of important diagnostic value, Dr. Swineford's statement to the contrary notwithstanding, and has prognostic value as well.

To urge that tests of pulmonary function take their place in the management of cardiopulmonary disease is not to say that the clinician's place is other than at the bedside. Armed with such "facts and figures" as laboratory studies can provide, he will apply the substance of this issue's article on cardiac asthma with even deeper understanding, with sharpened diagnostic acumen, and with better therapeutic results.

Announcements

New York Medical College Flower and Fifth Avenue Hospitals

The Division of Graduate Studies, Department of Graduate Pediatrics, announces a course in pediatric allergy to be given under the direction of Bret Ratner, M.D., Professor of Clinical Pediatrics and Associate Professor of Immunology. There will be thirty sessions, Wednesday 9 A.M. to 4 P.M., Nov. 6, 1957, to May 28, 1958. A fee of $300.00 will be charged.

The course consists of lecture-seminars, laboratory and clinical procedures, clinic work, and animal experimentation covering basic principles of diagnosis and treatment of allergy, and applied immunology in children.

Applicants must be certified in pediatrics or have the requirements for certification. A limited number of allergists practicing with adults may also apply.

Application should be made to the Office of the Dean, New York Medical College, Fifth Ave. at 106th St., New York 29, New York.

Philadelphia Allergy Society

The following officers have been elected for 1957 by the Philadelphia Allergy Society:

President, Edmund E. Ehrlich
Vice-President, Horace Pettit
Secretary-Treasurer, Eugene A. Hildreth

Dutch Allergy Society

With a view both to honoring the name of the great Dutch allergologist, Storm van Leeuwen, and expressing its great appreciation of the work done by other allergologists the Dutch Allergy Society has decided to institute the Storm van Leeuwen Medal. This medal will be awarded once every five years and the recipient will be invited to speak about his work. The Storm van Leeuwen Medal will be presented for the first time in May, 1958. In view of his splendid achievements in the field of allergology, the members of the Dutch Allergy Society have requested Dr. F. M. Rackemann of Boston, Massachusetts, to accept this medal.

Brazilian Allergy Society

The following are the officers elected on Dec. 19, 1956, by the Brazilian Allergy Society:

President, F. J. da Silveira Lobo, Jr.
Vice-President, Haroldo Cardoso de Castro
First Secretary, Paulo Dias da Costa
Second Secretary, Orlando Cavalcanti
Treasurer, A. N. Sayao Lobato
Historian, Clinio Pereira Lima

Venezuelan Society of Allergy

The following officers were elected on Feb. 1, 1957, by the Venezuelan Society of Allergy:

President, Marcel Granier
Vice-President, Francisco Kerdel Vegas
Secretary, Armando Perez Lozano
Treasurer, Luis Lozano Gomez
Historian, Lic. Zoraida Luces de Febres
Directors, Gabriel Trompiz and Carlos Benaim Pinto